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Committee for Medicinal Products for Human Use (CHMP)

Nimenrix

(meningococcal group a, c, w135 and y conjugate vaccine)

Procedure No. EMEA/H/C/000113/P46/0008
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CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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I. EXECUTIVE SUMMARY

This report includes six article 46 procedures submitted for Nimenrix.
P46 008 (MENACWY-TT-018 EXT:015 Y3) seq 11
P46 009 (MENACWY-TT-030 EXT:027 Y3) seq 12
P46 014 (MENACWY-TT-031 EXT 027 Y4) seq 19
P46 010 (MENACWY-TT-048 EXT: 039 Y2,3,4,5) seq 13
P46 011 (MENACWY-TT-071) seq 14
P46 012 (MENACWY-TT-057 PRI AND 057-BST) seq 15

The Company has provided data for these studies in this Article 46 procedure together with short clinical expert overviews for each. An overview of the submitted data is provided below consistent with the order presented in the report..
Data submitted for Article 46:

P46	Primary Study	Data submitted	eCTD sequence
P46 008	MenACWY-TT-015	MenACWY-TT-018 - year 3 follow-up of primary study (EXT: 015 Y3). Annex CSR plus clinical expert overview	11
P46 009	MenACWY-TT-027	MenACWY-TT-030 is a year 3 follow-up study of the primary study MenACWY-TT-027. Annex report 5 (December 2011) and Annex report 6 (Jan 2012) plus clinical expert overview.	12
P46 014	MenACWY-TT-027.	MenACWY-TT-031 is a year 4 follow-up study of the primary study. MenACWY-TT-031 EXT: 027 Y4) Annex Report 7 plus clinical expert overview.	19
P46 010	MenACWY-TT-039	MenACWY-TT-048 EXT 039 Y3 is a year 3 follow-up study of the primary study. Annex report Y3 plus clinical expert overview.	13
P46 011		MenACWY-TT-071 study is a stand alone study (full CSR) plus clinical expert overview	14
P46 012		MenACWY-TT-057 PRI & BST study is a stand alone study (full CSR) plus clinical expert overview.	15

The applicant states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product.

A variation application consisting of the full relevant data package (i.e containing several studies to update the labelling with available persistence data) is expected to be submitted by the beginning of 2013. No SmPC changes following this Article 46 Procedure are proposed.

II. RECOMMENDATION[1]

No SmPC and PL changes are proposed.

III. INTRODUCTION

Nimenrix is a quadrivalent meningococcal polysaccharide conjugate vaccines composed of Neisseria meningitides serogroups A, C, W-135, Y conjugated to tetanus toxoid. Nimenrix was authorised on 20th April 2012 for active immunisation of individuals from the age of 12 months and above against invasive meningococcal disease cause by Neisseria meningitides group A, C, W-135 and Y.
The data has been submitted in accordance with Article 46.

IV. SCIENTIFIC DISCUSSION

IV.1 Clinical aspects

Clinical studies

A synopsis of each study listed above is provided below.

1. P46 008
MENACWY-TT-018 EXT: 015 Y3 synopsis (seq 11)

Annex Clinical Study Report for Study 107402 (MENACWY-TT-018 EXT: 015 Y3) (Development Phase IIb)
A phase IIb, open, randomised, controlled primary vaccination study to evaluate the non-inferiority and the persistence of the immune response of GSK Biologicals' meningococcal serogroup ACWY conjugate vaccine given intramuscularly versus Mencevax ACWY given subcutaneously to healthy subjects aged 11 to 55 years of age.

Note: This study consists of two phases: the vaccination phase (107386 [MENACWYTT- 015]) and the long-term persistence phase 1 to 5 years after vaccination (studies 107392 [MENACWY-TT-016 EXT: 015 Y1]; 107398 [MENACWY-TT-017 EXT: 015 Y2]; 107402 [MENACWY-TT-018 EXT: 015 Y3]; 107404 [MENACWY-TT-019 EXT: 015 Y4] and 107406 [MENACWY-TT-020 EXT: 015 Y5], respectively). This report presents the persistence results 3 years after vaccination (107402 (MENACWY-TT-018 EXT: 015 Y3)). A full report describing the persistence results for years 1 through 5 after primary vaccination will be written when the results of the Year 5 persistence study are available.

Indication Studied: Primary immunisation of healthy subjects aged 11-55 years against meningococcal disease due to serogroup A, C, W-135 or Y.
Study initiation date of Year 3 persistence: 13 January 2010
Study completion date of Year 3 persistence: 24 August 2010
Data lock point: 29 March 2011
Date of Annex report: 23 February 2012
Earlier Study Reports
107386 (MENACWY-TT-015): 16 April 2009
107392 (MENACWY-TT-016 EXT 015 Y1): 30 June 2009
107398 (MENACWY-TT-017 EXT: 015 Y2): 08 April 2010
Study centre(s): This study was conducted at three centres (one in Saudi Arabia and two in the Philippines).

Objectives:
The primary objectives of the study were evaluated in study 107386 (MENACWY-TT-015).
Only the secondary objectives pertaining to this Year 3 persistence study are presented in this annex report.
Secondary:
Three years after vaccination:

- To compare the persistence of the immunogenicity of MenACWY-TT conjugate vaccine with that of the licensed *Mencevax* ACWY,
- To describe serious adverse events (SAEs) related to vaccination and any event related to lack of vaccine efficacy from 2 years up to 3 years after vaccination in a retrospective manner.

Study design:
The study is a Phase IIb, open, randomised (3:1), controlled, multi-centre, multi-country study with two parallel groups based on the vaccination received:

- ACWY-TT group: received one intramuscular (IM) dose of MenACWY-TT in the primary study 107386 (MENACWY-TT-015).
- MenPS group: received one subcutaneous dose of Mencevax ACWY in the primary study 107386 (MENACWY-TT-015).

A blood sample was collected from each subject 3 years after vaccination.

Number of subjects in 107402 (MENACWY-TT-018 EXT: 015 Y3)	ACWY-TT group	MenPS group	Total
Planned	374	126	500
Enrolled	344	116	460
Completed	344	116	460
Safety: Total Cohort Year 3	344	116	460
Immunogenicity: According-to-protocol (ATP) cohort for persistence Year 3	338	110	448

Diagnosis and criteria for inclusion: Healthy male or female subjects between and including 11 and 55 years of age at the time of vaccination, without a history of meningococcal serogroup A, C, W-135 or Y disease, who had not received a meningococcal polysaccharide vaccine for serogroups A, C, W-135 and/or Y within five years prior to enrolment in the primary study 107386 (MENACWY-TT-015) and who had never received a previous vaccination with meningococcal polysaccharide conjugate vaccine for serogroup A, C, W-135 and/or Y since birth.
Note: In case of vaccination with a meningococcal polysaccharide or a meningococcal polysaccharide conjugate vaccine since the study vaccine dose administered in study 107386 (MENACWY-TT-015), the subject was not to enter study 107402 (MENACWY-TT-018 EXT: 015 Y3) or any of the following years for antibody persistence assessment.

No vaccine was given in this persistence study.

Criteria for evaluation:

Immunogenicity:

Three years after vaccination (for evaluation of the persistence), in all evaluable subjects:

- Serum bactericidal assay/activity against *N. meningitidis* serogroups A, C, W-135 and Y using rabbit complement:rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8, ≥ 1:128 and GMTs. rSBA testing was done at a GSK laboratory.
- Anti-polysaccharide *N. meningitidis* serogroups A, C, W-135 and Y: anti-PSA, anti-PSC, anti-PSW-135 and anti-PSY concentrations ≥ 0.3 μg/mL, ≥ 2.0 μg/mL and GMCs.

Reactogenicity and Safety:

- Occurrence of SAEs (including cases of invasive meningococcal disease) related to vaccination and any event related to lack of vaccine efficacy from the last study contact (Visit 5/Month 24) of the study 107398 (MENACWY-TT-017 EXT: 015 Y2) up to the Year 3 follow-up visit (Visit 6/Month 36)*.

***Note:** At Year 3 of the long-term persistence phase the subject/subject's parents/LARs were asked retrospectively if any SAE, as defined hereafter, had occurred since the Month 24 visit of study 107398 (MENACWY-TT-017 EXT: 015 Y2). Only those SAEs that were determined by the investigator to have a causal relationship to the vaccination were described individually in the study report, along with the nature of the SAEs and the outcome. Any event related to lack of vaccine efficacy (i.e. meningococcal disease) during the Year 3 long-term persistence phase or related to study participation were described in detail.

Results:

Immunogenicity results:

The analysis was performed on the ATP cohort for persistence Year 3. The percentage of subjects with Year 3 serological results excluded from the ATP cohort was higher than 5% in the MenPS group. Therefore a second analysis based on the Total Cohort Year 3 was performed to complement the ATP analysis. Similar results were observed in both cohorts.

The percentages of subjects with rSBA titres ≥ 1:8 and ≥ 1:128 and rSBA GMTs are summarised in Synopsis Table 1.

- 99.1% (rSBA-MenC) to 100% (rSBA-MenA) of the subjects in the ACWY-TT group had an rSBA antibody titre ≥ 1:8. 86.7% (rSBA-MenW-135) to 100% (rSBA-MenA) of the subjects in the MenPS group had an rSBA antibody titre ≥ 1:8.
- 92.9% (rSBA-MenC) to 99.4% (rSBA-MenY) of the subjects in the ACWY-TT group had an rSBA antibody titre ≥ 1:128. 80.0% (rSBA-MenW-135) to 97.2% (rSBA-MenY) of the subjects in the MenPS group had an rSBA antibody titre ≥ 1:128.
- For all the four serogroups, the observed rSBA GMT values at Month 36 (Year 3) exceeded the levels observed at the pre-vaccination time-point in both groups. rSBA GMTs in the ACWY-TT group ranged from 870.3 (rSBA-MenC) to 2567.3 (rSBA-MenY). In the MenPS group rSBA GMTs ranged from 332.8 (rSBA-MenW-135) to 1124.8 (rSBA-MenC).

The exploratory group comparisons suggested:

- A higher percentage of subjects with rSBA-MenW-135 ≥1:8 in the ACWY-TT group compared to the MenPS group.
- A higher percentage of subjects with rSBA-MenA and rSBA-MenW-135 ≥1:128 in the ACWY-TT group compared to the MenPS group.
- Higher rSBA-MenA, rSBA-MenW-135 and rSBA-MenY GMTs at Year 3 in the ACWY-TT group compared to the MenPS group.

The findings per age stratum were generally similar with those of the entire study population.

Synopsis Table 1 Percentage of subjects with rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs (ATP cohort for persistence Year 3)

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenA	ACWY-TT	PRE	304	289	95.1	92.0	97.2	273	89.8	85.8	93.0	336.3	290.2	389.7
		PI(M1)	324	324	100	98.9	100	323	99.7	98.3	100	4924.4	4429.7	5474.4
		PI(M12)	334	333	99.7	98.3	100	332	99.4	97.9	99.9	2116.6	1910.8	2344.7
		PI(M24)	324	323	99.7	98.3	100	321	99.1	97.3	99.8	1342.5	1209.4	1490.3
		PI(M36)	322	322	100	98.9	100	319	99.1	97.3	99.8	1238.4	1126.0	1361.9
	MenPS	PRE	96	83	86.5	78.0	92.6	75	78.1	68.5	85.9	219.8	153.5	314.9
		PI(M1)	107	107	100	96.6	100	106	99.1	94.9	100	2146.3	1799.9	2559.4
		PI(M12)	106	106	100	96.6	100	105	99.1	94.9	100	1123.4	943.8	1337.2
		PI(M24)	97	96	99.0	94.4	100	93	95.9	89.8	98.9	695.8	553.1	875.4
		PI(M36)	104	104	100	96.5	100	98	94.2	87.9	97.9	596.9	488.5	729.3
rSBA-MenC	ACWY-TT	PRE	321	249	77.6	72.6	82.0	166	51.7	46.1	57.3	83.4	67.7	102.7
		PI(M1)	338	337	99.7	98.4	100	335	99.1	97.4	99.8	9155.8	7840.9	10691.3
		PI(M12)	333	332	99.7	98.3	100	324	97.3	94.9	98.8	1878.5	1637.2	2155.4
		PI(M24)	332	330	99.4	97.8	99.9	320	96.4	93.8	98.1	1164.3	1014.2	1336.7
		PI(M36)	337	334	99.1	97.4	99.8	313	92.9	89.6	95.4	870.3	757.1	1000.4
	MenPS	PRE	109	92	84.4	76.2	90.6	56	51.4	41.6	61.1	113.4	79.3	162.3
		PI(M1)	110	110	100	96.7	100	107	97.3	92.2	99.4	6116.0	4658.1	8030.2
		PI(M12)	108	106	98.1	93.5	99.8	103	95.4	89.5	98.5	1926.9	1395.7	2660.2
		PI(M24)	107	104	97.2	92.0	99.4	97	90.7	83.5	95.4	1186.9	821.7	1714.3
		PI(M36)	109	108	99.1	95.0	100	102	93.6	87.2	97.4	1124.8	812.3	1557.6
rSBA-MenW-135	ACWY-TT	PRE	323	247	76.5	71.5	81.0	191	59.1	53.6	64.5	98.6	79.1	122.9
		PI(M1)	337	336	99.7	98.4	100	335	99.4	97.9	99.9	8568.5	7594.2	9667.9
		PI(M12)	336	335	99.7	98.4	100	334	99.4	97.9	99.9	3056.0	2661.0	3509.6
		PI(M24)	333	331	99.4	97.8	99.9	329	98.8	97.0	99.7	1997.8	1765.4	2260.8
		PI(M36)	336	335	99.7	98.4	100	332	98.8	97.0	99.7	2109.2	1842.5	2414.5
	MenPS	PRE	105	85	81.0	72.1	88.0	64	61.0	50.9	70.3	111.7	78.2	159.4
		PI(M1)	110	110	100	96.7	100	110	100	96.7	100	3057.7	2507.6	3728.5
		PI(M12)	110	110	100	96.7	100	104	94.5	88.5	98.0	713.9	574.7	886.9
		PI(M24)	106	95	89.6	82.2	94.7	85	80.2	71.3	87.3	319.5	224.9	454.1
		PI(M36)	105	91	86.7	78.6	92.5	84	80.0	71.1	87.2	332.8	224.4	493.8

Table 1 continues on the next page

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenY	ACWY-TT	PRE	328	304	92.7	89.3	95.3	262	79.9	75.1	84.1	308.5	259.9	366.0
		PI(M1)	337	337	100	98.9	100	336	99.7	98.4	100	10788.8	9714.7	11981.5
		PI(M12)	335	335	100	98.9	100	334	99.7	98.3	100	4373.3	3905.9	4896.7
		PI(M24)	333	332	99.7	98.3	100	330	99.1	97.4	99.8	3100.2	2736.2	3512.6
		PI(M36)	338	337	99.7	98.4	100	336	99.4	97.9	99.9	2567.3	2288.6	2879.8
	MenPS	PRE	109	102	93.6	87.2	97.4	86	78.9	70.0	86.1	310.9	230.9	418.6
		PI(M1)	110	110	100	96.7	100	110	100	96.7	100	4824.2	4066.8	5722.6
		PI(M12)	109	109	100	96.7	100	108	99.1	95.0	100	1466.6	1181.1	1821.1
		PI(M24)	106	106	100	96.6	100	102	96.2	90.6	99.0	909.9	729.9	1134.3
		PI(M36)	108	107	99.1	94.9	100	105	97.2	92.1	99.4	848.0	682.6	1053.5

ACWY-TT = MenACWY-TT; MenPS = Mencevax ACWY
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Month 0; PI(M1) = Post-vaccination at Month 1; PI(M12) = Post-vaccination at Year 1
PI(M24) = Post-vaccination at Year 2; PI(M36) = Post-vaccination at Year 3

The percentages of subjects with anti-PS concentrations ≥ 0.3 μg/mL and ≥ 2.0 μg/mL and anti-PS GMCs
are summarised in Synopsis Table 2.

- 92.4% (Anti-PSW-135) to 99.4% (Anti-PSA) of the subjects in the ACWY-TT group had an Anti-PS concentration ≥ 0.3 μg/mL. 97.2% (Anti-PSW-135) to 100% (Anti-PSA and Anti-PSC) of the subjects in the MenPS group had an Anti-PS concentration ≥ 0.3 μg/mL.
- 60.4% (Anti-PSC) to 90.9% (Anti-PSA) of the subjects in the ACWY-TT group had an Anti-PS concentration ≥ 2 μg/mL. 80.6% (Anti-PSW-135) to 99.1% (Anti-PSA) of the subjects in the MenPS group had an Anti-PS concentration ≥ 2 μg/mL.
- The observed GMC values for all anti-PS antibodies at Month 36 (Year 3) exceeded the levels observed at the pre-vaccination time-point in both groups. Anti-PS GMCs in the ACWY-TT group ranged from 2.7 (Anti-PSC) to 12.5 (Anti-PSA). In the MenPS group anti-PS GMCs ranged from 5.5 (Anti-PSW-135) to 19.8 (Anti-PSA).

The exploratory group comparisons suggested:

- A higher percentage of subjects with Anti-PSC and Anti-PSY ≥ 0.3 μg/mL in the MenPS group compared to the ACWY-TT group.
- A higher percentage of subjects ≥ 2 μg/mL for all anti-PS antibodies in the MenPS group compared to the ACWY-TT group.
- Higher GMCs for all anti-PS antibodies in the MenPS group compared to the ACWY-TT group.

The findings per age stratum were generally similar with those of the entire study population.

Synopsis Table 2 Percentage of subjects with Anti-PS concentrations equal to or above the cut-off values of 0.3 microgram/mL and 2.0 microgram/mL and GMCs (ATP cohort for persistence Year 3)

				≥ 0.3 µg/mL				≥ 2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-PSA	ACWY-TT	PRE	307	249	81.1	76.3	85.3	135	44.0	38.3	49.7	1.5	1.3	1.8
		PI(M1)	337	336	99.7	98.4	100	336	99.7	98.4	100	105.5	91.1	122.1
		PI(M12)	333	332	99.7	98.3	100	313	94.0	90.9	96.3	22.3	18.9	26.3
		PI(M24)	322	321	99.7	98.3	100	287	89.1	85.2	92.3	14.9	12.5	17.8
		PI(M36)	330	328	99.4	97.8	99.9	300	90.9	87.3	93.8	12.5	10.7	14.6
	MenPS	PRE	103	86	83.5	74.9	90.1	51	49.5	39.5	59.5	1.8	1.3	2.5
		PI(M1)	109	109	100	96.7	100	109	100	96.7	100	57.6	44.7	74.1
		PI(M12)	109	109	100	96.7	100	108	99.1	95.0	100	35.1	27.3	45.0
		PI(M24)	100	100	100	96.4	100	98	98.0	93.0	99.8	26.4	20.2	34.6
		PI(M36)	109	109	100	96.7	100	108	99.1	95.0	100	19.8	15.7	24.9
Anti-PSC	ACWY-TT	PRE	328	80	24.4	19.8	29.4	36	11.0	7.8	14.9	0.3	0.2	0.3
		PI(M1)	338	337	99.7	98.4	100	331	97.9	95.8	99.2	24.1	21.2	27.5
		PI(M12)	334	330	98.8	97.0	99.7	246	73.7	68.6	78.3	4.6	4.0	5.3
		PI(M24)	327	310	94.8	91.8	96.9	185	56.6	51.0	62.0	2.6	2.2	3.0
		PI(M36)	331	318	96.1	93.4	97.9	200	60.4	54.9	65.7	2.7	2.3	3.0
	MenPS	PRE	106	28	26.4	18.3	35.9	17	16.0	9.6	24.4	0.3	0.3	0.5
		PI(M1)	110	110	100	96.7	100	109	99.1	95.0	100	43.3	35.5	52.9
		PI(M12)	110	110	100	96.7	100	107	97.3	92.2	99.4	26.3	21.3	32.6
		PI(M24)	106	106	100	96.6	100	102	96.2	90.6	99.0	16.2	12.8	20.5
		PI(M36)	110	110	100	96.7	100	106	96.4	91.0	99.0	13.9	11.2	17.2
Anti-PSW-135	ACWY-TT	PRE	322	42	13.0	9.6	17.2	11	3.4	1.7	6.0	0.2	0.2	0.2
		PI(M1)	336	332	98.8	97.0	99.7	311	92.6	89.2	95.1	19.1	16.2	22.5
		PI(M12)	329	323	98.2	96.1	99.3	248	75.4	70.4	79.9	5.5	4.7	6.5
		PI(M24)	323	302	93.5	90.2	95.9	218	67.5	62.1	72.6	3.5	2.9	4.1
		PI(M36)	328	303	92.4	89.0	95.0	204	62.2	56.7	67.5	2.9	2.5	3.4
	MenPS	PRE	101	16	15.8	9.3	24.4	3	3.0	0.6	8.4	0.2	0.2	0.3
		PI(M1)	110	110	100	96.7	100	106	96.4	91.0	99.0	17.0	13.2	21.9
		PI(M12)	108	107	99.1	94.9	100	98	90.7	83.6	95.5	11.5	8.7	15.1
		PI(M24)	106	105	99.1	94.9	100	91	85.8	77.7	91.9	7.4	5.6	9.8
		PI(M36)	108	105	97.2	92.1	99.4	87	80.6	71.8	87.5	5.5	4.2	7.2
Anti-PSY	ACWY-TT	PRE	322	54	16.8	12.9	21.3	23	7.1	4.6	10.5	0.2	0.2	0.3
		PI(M1)	336	335	99.7	98.4	100	325	96.7	94.2	98.4	24.9	21.4	29.0
		PI(M12)	334	330	98.8	97.0	99.7	274	82.0	77.5	86.0	6.7	5.6	7.8
		PI(M24)	330	314	95.2	92.2	97.2	227	68.8	63.5	73.8	4.4	3.7	5.3
		PI(M36)	323	299	92.6	89.1	95.2	213	65.9	60.5	71.1	3.8	3.2	4.5

Table 2 continues on the next page

				≥ 0.3 µg/mL				≥ 2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-PSY	MenPS	PRE	106	23	21.7	14.3	30.8	10	9.4	4.6	16.7	0.3	0.2	0.3
		PI(M1)	108	108	100	96.6	100	106	98.1	93.5	99.8	24.8	19.4	31.6
		PI(M12)	109	109	100	96.7	100	105	96.3	90.9	99.0	17.4	13.4	22.5
		PI(M24)	107	105	98.1	93.4	99.8	94	87.9	80.1	93.4	11.6	8.8	15.4
		PI(M36)	110	108	98.2	93.6	99.8	92	83.6	75.4	90.0	8.2	6.2	10.8

ACWY-TT = MenACWY-TT; MenPS = Mencevax ACWY
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Month 0; PI(M1) = Post-vaccination at Month 1; PI(M12) = Post-vaccination at Year 1
PI(M24) = Post-vaccination at Year 2; PI(M36) = Post-vaccination at Year 3

Robustness analysis & predictive modelling
For rSBA and anti-PS, the exploratory analyses that take into account the effect of drop outs with or without assuming any type of decay are in line with the analyses that ignore drop-out.
The predicted GMTs were similar to the observed values for the Year 3 Total Vaccinated Cohort. The findings per age stratum were generally similar with those of the entire study population.
Safety /reactogenicity: No SAEs considered related to vaccination or events related to the lack of vaccine efficacy were reported since the second persistence visit (2 years after vaccination) up to the third persistence visit (3 years after vaccination).
Two complete abortions and one ectopic pregnancy were reported although these events are not vaccine related nor a case of lack of vaccine efficacy.

MAH Conclusions:
This study evaluated the persistence of the immune response and the occurrence of SAEs related to
vaccination and events related to lack of vaccine efficacy up to 3 years after vaccination with the
MenACWY-TT candidate vaccine or the *Mencevax* ACWY control vaccine in the 107386 (MENACWYTT-015) study.
Three years after vaccination for rSBA:
- At least 99.1% of the subjects had rSBA titres ≥1:8 for all four serogroups in both study groups
except for rSBA-MenW-135 in the MenPS group (86.7%).
- At least 92.9% and 80.0% of the subjects in the ACWY-TT and MenPS groups respectively, retained
rSBA titres ≥1:128 for all four serogroups.
- GMTs ranged between 870.3 (rSBA-MenC) and 2567.3 (rSBA-MenY) in the ACWY-TT group and between 332.8 (rSBA-MenW-135) and 1124.8 (rSBA-MenC) in the MenPS group.
- No SAEs assessed by the investigator as related to vaccination or any events related to lack of
vaccine efficacy were reported from the last visit of the vaccination phase (6 months after vaccination) up to the third persistence visit (3 years after vaccination).

No confirmatory analyses were performed on secondary objectives.

Assessor's comment: Non-inferiority for Nimenrix compared with MenPS holds at year 3 for all the data shown above with the exception of GMT for Men C. However the GMTs are still well above baseline and the majority of titres are above 1:128.
It is noted that the rSBA at GSK was compared to the rSBA performed at the HPA at year 2 (discussed in D180 report for initial MAA). It was noted that the GSK results were higher than the results from the HPA, but even so the post-vaccination difference between groups still favoured Nimenrix.

The data was analysed by age stratum and the company conclusion that the results were generally similar is agreed. The results by age stratum are provided in the two supplementary tables below.

Supplement 24 Percentage of subjects with rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs, per age strata (ATP cohort for persistence Year 3)

					≥ 1:8				≥ 1:128				GMT		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenA	ACWY-TT	11-17y	PRE	203	196	96.6	93.0	98.6	188	92.6	88.1	95.8	378.5	322.7	444.0
			PI(M1)	211	211	100	98.3	100	211	100	98.3	100	5498.5	4838.2	6248.8
			PI(M12)	220	220	100	98.3	100	219	99.5	97.5	100	2373.8	2116.3	2662.5
			PI(M24)	215	215	100	98.3	100	215	100	98.3	100	1505.7	1338.7	1693.6
			PI(M36)	215	215	100	98.3	100	214	99.5	97.4	100	1412.4	1265.2	1576.7
		18-55y	PRE	101	93	92.1	85.0	96.5	85	84.2	75.6	90.7	265.1	195.2	360.0
			PI(M1)	113	113	100	96.8	100	112	99.1	95.2	100	4008.1	3334.5	4817.7
			PI(M12)	114	113	99.1	95.2	100	113	99.1	95.2	100	1696.5	1391.4	2068.5
			PI(M24)	109	108	99.1	95.0	100	106	97.2	92.2	99.4	1070.6	874.4	1310.8
			PI(M36)	107	107	100	96.6	100	105	98.1	93.4	99.8	950.8	799.5	1130.9
	MenPS	11-17y	PRE	67	62	92.5	83.4	97.5	59	88.1	77.8	94.7	319.9	223.9	456.9
			PI(M1)	74	74	100	95.1	100	74	100	95.1	100	2640.8	2180.6	3198.0
			PI(M12)	76	76	100	95.3	100	76	100	95.3	100	1226.3	1000.2	1503.6
			PI(M24)	67	66	98.5	92.0	100	66	98.5	92.0	100	808.0	618.2	1056.2
			PI(M36)	70	70	100	94.9	100	68	97.1	90.1	99.7	721.5	565.7	920.2
		18-55y	PRE	29	21	72.4	52.8	87.3	16	55.2	35.7	73.6	92.4	41.1	207.6
			PI(M1)	33	33	100	89.4	100	32	97.0	84.2	99.9	1348.3	960.7	1892.2
			PI(M12)	30	30	100	88.4	100	29	96.7	82.8	99.9	899.6	639.7	1265.2
			PI(M24)	30	30	100	88.4	100	27	90.0	73.5	97.9	498.3	321.2	773.1
			PI(M36)	34	34	100	89.7	100	30	88.2	72.5	96.7	404.1	290.0	563.0
rSBA-MenC	ACWY-TT	11-17y	PRE	207	155	74.9	68.4	80.6	104	50.2	43.2	57.2	74.4	57.1	97.0
			PI(M1)	221	220	99.5	97.5	100	220	99.5	97.5	100	10608.3	8915.3	12622.8
			PI(M12)	220	219	99.5	97.5	100	215	97.7	94.8	99.3	1943.7	1639.8	2304.0
			PI(M24)	220	219	99.5	97.5	100	215	97.7	94.8	99.3	1147.6	980.5	1343.2
			PI(M36)	221	219	99.1	96.8	99.9	205	92.8	88.5	95.8	902.3	759.8	1071.4
		18-55y	PRE	114	94	82.5	74.2	88.9	62	54.4	44.8	63.7	102.4	72.8	144.0
			PI(M1)	117	117	100	96.9	100	115	98.3	94.0	99.8	6932.8	5126.1	9376.2
			PI(M12)	113	113	100	96.8	100	109	96.5	91.2	99.0	1757.8	1387.3	2227.2
			PI(M24)	112	111	99.1	95.1	100	105	93.8	87.5	97.5	1198.0	913.0	1571.8
			PI(M36)	116	115	99.1	95.3	100	108	93.1	86.9	97.0	812.6	638.5	1034.0
	MenPS	11-17y	PRE	75	59	78.7	67.7	87.3	38	50.7	38.9	62.4	105.4	65.5	169.5
			PI(M1)	76	76	100	95.3	100	74	97.4	90.8	99.7	6112.2	4352.7	8582.9
			PI(M12)	74	73	98.6	92.7	100	72	97.3	90.6	99.7	1758.5	1200.8	2575.1
			PI(M24)	75	73	97.3	90.7	99.7	68	90.7	81.7	96.2	986.2	635.8	1529.8
			PI(M36)	76	75	98.7	92.9	100	71	93.4	85.3	97.8	995.0	657.7	1505.2
		18-55y	PRE	34	33	97.1	84.7	99.9	18	52.9	35.1	70.2	133.5	81.1	219.8
			PI(M1)	34	34	100	89.7	100	33	97.1	84.7	99.9	6124.5	3814.2	9834.4
			PI(M12)	34	33	97.1	84.7	99.9	31	91.2	76.3	98.1	2351.3	1258.3	4393.6
			PI(M24)	32	31	96.9	83.8	99.9	29	90.6	75.0	98.0	1831.9	922.7	3637.1
			PI(M36)	33	33	100	89.4	100	31	93.9	79.8	99.3	1492.1	891.3	2497.7

					≥ 1:8				≥ 1:128				GMT		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenW-135	ACWY-TT	11-17y	PRE	213	168	78.9	72.8	84.2	141	66.2	59.4	72.5	122.5	94.1	159.3
			PI(M1)	220	219	99.5	97.5	100	218	99.1	96.8	99.9	10523.5	9133.4	12125.1
			PI(M12)	221	220	99.5	97.5	100	220	99.5	97.5	100	3705.0	3135.1	4378.6
			PI(M24)	221	220	99.5	97.5	100	219	99.1	96.8	99.9	2216.5	1916.4	2563.6
			PI(M36)	221	220	99.5	97.5	100	219	99.1	96.8	99.9	2507.7	2141.1	2937.2
		18-55y	PRE	110	79	71.8	62.4	80.0	50	45.5	35.9	55.2	64.9	43.8	96.1
			PI(M1)	117	117	100	96.9	100	117	100	96.9	100	5822.1	4725.4	7173.3
			PI(M12)	115	115	100	96.8	100	114	99.1	95.3	100	2110.6	1669.2	2668.7
			PI(M24)	112	111	99.1	95.1	100	110	98.2	93.7	99.8	1627.4	1295.3	2044.7
			PI(M36)	115	115	100	96.8	100	113	98.3	93.9	99.8	1512.5	1184.5	1931.2
	MenPS	11-17y	PRE	72	61	84.7	74.3	92.1	49	68.1	56.0	78.6	142.5	94.4	215.0
			PI(M1)	76	76	100	95.3	100	76	100	95.3	100	3548.7	2837.0	4438.9
			PI(M12)	76	76	100	95.3	100	72	94.7	87.1	98.5	775.6	599.3	1003.8
			PI(M24)	74	65	87.8	78.2	94.3	60	81.1	70.3	89.3	300.9	195.7	462.7
			PI(M36)	73	63	86.3	76.2	93.2	58	79.5	68.4	88.0	348.9	215.7	564.4
		18-55y	PRE	33	24	72.7	54.5	86.7	15	45.5	28.1	63.6	65.6	33.0	130.5
			PI(M1)	34	34	100	89.7	100	34	100	89.7	100	2191.9	1474.1	3259.2
			PI(M12)	34	34	100	89.7	100	32	94.1	80.3	99.3	593.2	392.2	897.2
			PI(M24)	32	30	93.8	79.2	99.2	25	78.1	60.0	90.7	367.2	194.1	694.4
			PI(M36)	32	28	87.5	71.0	96.5	26	81.3	63.6	92.8	298.9	144.7	617.4
rSBA-MenY	ACWY-TT	11-17y	PRE	214	200	93.5	89.3	96.4	183	85.5	80.1	89.9	369.4	300.9	453.6
			PI(M1)	220	220	100	98.3	100	219	99.5	97.5	100	12529.6	11168.8	14056.2
			PI(M12)	220	220	100	98.3	100	219	99.5	97.5	100	4930.5	4290.1	5666.5
			PI(M24)	221	220	99.5	97.5	100	218	98.6	96.1	99.7	3162.4	2704.1	3698.4
			PI(M36)	221	220	99.5	97.5	100	220	99.5	97.5	100	2941.7	2551.9	3391.0
		18-55y	PRE	114	104	91.2	84.5	95.7	79	69.3	60.0	77.6	219.9	162.7	297.2
			PI(M1)	117	117	100	96.9	100	117	100	96.9	100	8143.6	6642.2	9984.2
			PI(M12)	115	115	100	96.8	100	115	100	96.8	100	3476.8	2876.3	4202.6
			PI(M24)	112	112	100	96.8	100	112	100	96.8	100	2980.9	2418.2	3674.5
			PI(M36)	117	117	100	96.9	100	116	99.1	95.3	100	1985.1	1642.9	2398.6
	MenPS	11-17y	PRE	75	72	96.0	88.8	99.2	66	88.0	78.4	94.4	431.1	313.4	593.1
			PI(M1)	76	76	100	95.3	100	76	100	95.3	100	5103.0	4197.2	6204.4
			PI(M12)	75	75	100	95.2	100	75	100	95.2	100	1660.0	1289.7	2136.4
			PI(M24)	74	74	100	95.1	100	71	95.9	88.6	99.2	949.5	726.9	1240.2
			PI(M36)	76	76	100	95.3	100	76	100	95.3	100	978.1	780.3	1226.0
		18-55y	PRE	34	30	88.2	72.5	96.7	20	58.8	40.7	75.4	151.2	83.1	274.9
			PI(M1)	34	34	100	89.7	100	34	100	89.7	100	4254.7	2995.3	6043.8
			PI(M12)	34	34	100	89.7	100	33	97.1	84.7	99.9	1116.0	733.5	1697.9
			PI(M24)	32	32	100	89.1	100	31	96.9	83.8	99.9	824.6	547.1	1242.7
			PI(M36)	32	31	96.9	83.8	99.9	29	90.6	75.0	98.0	604.3	366.1	997.5

ACWY-TT = MenACWY-TT; MenPS = Mencevax ACWY
11-17y = subjects below 18 years of age
18-55y = subjects of 18 years of age and above
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Month 0
PI(M1) = Post-vaccination at Month 1
PI(M12) = Post-vaccination at Year 1
PI(M24) = Post-vaccination at Year 2
PI(M36) = Post-vaccination at Year 3

Supplement 25 Percentage of subjects with Anti-PS concentrations equal to or above the cut-off values of 0.3 microgram/mL and 2.0 microgram/mL and GMCs, per age strata (ATP cohort for persistence Year 3)

					≥ 0.3 µg/mL				≥ 2 µg/mL				GMC		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-PSA	ACWY-TT	11-17y	PRE	207	162	78.3	72.0	83.7	76	36.7	30.1	43.7	1.15	0.94	1.42
			PI(M1)	220	219	99.5	97.5	100	219	99.5	97.5	100	104.97	87.98	125.23
			PI(M12)	220	219	99.5	97.5	100	204	92.7	88.5	95.8	17.75	14.48	21.75
			PI(M24)	215	214	99.5	97.4	100	188	87.4	82.3	91.6	11.91	9.62	14.75
			PI(M36)	213	212	99.5	97.4	100	192	90.1	85.3	93.8	11.16	9.24	13.48
		18-55y	PRE	100	87	87.0	78.8	92.9	59	59.0	48.7	68.7	2.59	1.85	3.64
			PI(M1)	117	117	100	96.9	100	117	100	96.9	100	106.44	81.73	138.61
			PI(M12)	113	113	100	96.8	100	109	96.5	91.2	99.0	34.69	26.31	45.75
			PI(M24)	107	107	100	96.6	100	99	92.5	85.8	96.7	23.41	17.31	31.67
			PI(M36)	117	116	99.1	95.3	100	108	92.3	85.9	96.4	15.37	11.63	20.32
	MenPS	11-17y	PRE	70	58	82.9	72.0	90.8	35	50.0	37.8	62.2	1.72	1.18	2.49
			PI(M1)	75	75	100	95.2	100	75	100	95.2	100	65.62	49.72	86.60
			PI(M12)	76	76	100	95.3	100	75	98.7	92.9	100	37.63	28.47	49.73
			PI(M24)	72	72	100	95.0	100	71	98.6	92.5	100	28.28	20.97	38.13
			PI(M36)	76	76	100	95.3	100	75	98.7	92.9	100	20.02	15.26	26.28
		18-55y	PRE	33	28	84.8	68.1	94.9	16	48.5	30.8	66.5	2.04	1.08	3.82
			PI(M1)	34	34	100	89.7	100	34	100	89.7	100	43.10	24.99	74.34
			PI(M12)	33	33	100	89.4	100	33	100	89.4	100	29.81	17.45	50.92
			PI(M24)	28	28	100	87.7	100	27	96.4	81.7	99.9	22.27	12.18	40.70
			PI(M36)	33	33	100	89.4	100	33	100	89.4	100	19.25	12.15	30.51
Anti-PSC	ACWY-TT	11-17y	PRE	217	43	19.8	14.7	25.7	17	7.8	4.6	12.2	0.24	0.21	0.28
			PI(M1)	221	220	99.5	97.5	100	220	99.5	97.5	100	32.54	27.94	37.89
			PI(M12)	219	216	98.6	96.0	99.7	158	72.1	65.7	78.0	4.43	3.74	5.26
			PI(M24)	216	205	94.9	91.1	97.4	116	53.7	46.8	60.5	2.37	1.97	2.85
			PI(M36)	217	208	95.9	92.3	98.1	132	60.8	54.0	67.4	2.66	2.26	3.14
		18-55y	PRE	111	37	33.3	24.7	42.9	19	17.1	10.6	25.4	0.38	0.29	0.50
			PI(M1)	117	117	100	96.9	100	111	94.9	89.2	98.1	13.72	11.06	17.02
			PI(M12)	115	114	99.1	95.3	100	88	76.5	67.7	83.9	5.02	3.97	6.35
			PI(M24)	111	105	94.6	88.6	98.0	69	62.2	52.5	71.2	2.98	2.33	3.80
			PI(M36)	114	110	96.5	91.3	99.0	68	59.6	50.1	68.7	2.68	2.16	3.32
	MenPS	11-17y	PRE	74	15	20.3	11.8	31.2	7	9.5	3.9	18.5	0.26	0.20	0.34
			PI(M1)	76	76	100	95.3	100	75	98.7	92.9	100	40.97	32.54	51.57
			PI(M12)	76	76	100	95.3	100	73	96.1	88.9	99.2	22.12	17.00	28.78
			PI(M24)	74	74	100	95.1	100	70	94.6	86.7	98.5	13.51	10.13	18.00
			PI(M36)	76	76	100	95.3	100	72	94.7	87.1	98.5	11.39	8.82	14.72
		18-55y	PRE	32	13	40.6	23.7	59.4	10	31.3	16.1	50.0	0.63	0.31	1.28
			PI(M1)	34	34	100	89.7	100	34	100	89.7	100	49.15	32.74	73.78
			PI(M12)	34	34	100	89.7	100	34	100	89.7	100	38.91	27.36	55.33
			PI(M24)	32	32	100	89.1	100	32	100	89.1	100	24.60	16.64	36.37
			PI(M36)	34	34	100	89.7	100	34	100	89.7	100	21.56	14.85	31.32

					≥ 0.3 µg/mL				≥ 2 µg/mL				GMC		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-PSW-135	ACWY-TT	11-17y	PRE	218	23	10.6	6.8	15.4	6	2.8	1.0	5.9	0.19	0.17	0.21
			PI(M1)	220	217	98.6	96.1	99.7	206	93.6	89.6	96.5	18.61	15.31	22.62
			PI(M12)	217	212	97.7	94.7	99.2	163	75.1	68.8	80.7	5.23	4.28	6.39
			PI(M24)	214	197	92.1	87.6	95.3	142	66.4	59.6	72.7	3.03	2.47	3.71
			PI(M36)	214	196	91.6	87.0	94.9	132	61.7	54.8	68.2	2.62	2.16	3.19
		18-55y	PRE	104	19	18.3	11.4	27.1	5	4.8	1.6	10.9	0.22	0.18	0.27
			PI(M1)	116	115	99.1	95.3	100	105	90.5	83.7	95.2	20.10	14.90	27.13
			PI(M12)	112	111	99.1	95.1	100	85	75.9	66.9	83.5	6.10	4.62	8.07
			PI(M24)	109	105	96.3	90.9	99.0	76	69.7	60.2	78.2	4.62	3.40	6.27
			PI(M36)	114	107	93.9	87.8	97.5	72	63.2	53.6	72.0	3.54	2.66	4.71
	MenPS	11-17y	PRE	72	11	15.3	7.9	25.7	1	1.4	0.0	7.5	0.20	0.17	0.23
			PI(M1)	76	76	100	95.3	100	73	96.1	88.9	99.2	15.74	11.58	21.42
			PI(M12)	74	74	100	95.1	100	69	93.2	84.9	97.8	11.65	8.52	15.95
			PI(M24)	74	74	100	95.1	100	64	86.5	76.5	93.3	6.67	4.88	9.10
			PI(M36)	74	72	97.3	90.6	99.7	59	79.7	68.8	88.2	5.07	3.70	6.94
		18-55y	PRE	29	5	17.2	5.8	35.8	2	6.9	0.8	22.8	0.25	0.15	0.40
			PI(M1)	34	34	100	89.7	100	33	97.1	84.7	99.9	20.29	12.79	32.20
			PI(M12)	34	33	97.1	84.7	99.9	29	85.3	68.9	95.0	11.16	6.36	19.56
			PI(M24)	32	31	96.9	83.8	99.9	27	84.4	67.2	94.7	9.31	5.00	17.33
			PI(M36)	34	33	97.1	84.7	99.9	28	82.4	65.5	93.2	6.53	3.77	11.30
Anti-PSY	ACWY-TT	11-17y	PRE	217	33	15.2	10.7	20.7	15	6.9	3.9	11.1	0.22	0.19	0.26
			PI(M1)	220	219	99.5	97.5	100	215	97.7	94.8	99.3	23.57	19.77	28.10
			PI(M12)	221	219	99.1	96.8	99.9	181	81.9	76.2	86.7	5.97	4.91	7.25
			PI(M24)	218	207	95.0	91.2	97.5	148	67.9	61.3	74.0	3.89	3.16	4.78
			PI(M36)	210	193	91.9	87.4	95.2	137	65.2	58.4	71.7	3.36	2.74	4.12
		18-55y	PRE	105	21	20.0	12.8	28.9	8	7.6	3.3	14.5	0.23	0.19	0.28
			PI(M1)	116	116	100	96.9	100	110	94.8	89.1	98.1	27.64	20.67	36.96
			PI(M12)	113	111	98.2	93.8	99.8	93	82.3	74.0	88.8	8.22	6.05	11.15
			PI(M24)	112	107	95.5	89.9	98.5	79	70.5	61.2	78.8	5.59	3.99	7.82
			PI(M36)	113	106	93.8	87.7	97.5	76	67.3	57.8	75.8	4.70	3.43	6.45
	MenPS	11-17y	PRE	73	11	15.1	7.8	25.4	5	6.8	2.3	15.3	0.23	0.17	0.31
			PI(M1)	75	75	100	95.2	100	75	100	95.2	100	26.24	20.39	33.76
			PI(M12)	76	76	100	95.3	100	74	97.4	90.8	99.7	17.37	13.09	23.05
			PI(M24)	75	75	100	95.2	100	67	89.3	80.1	95.3	11.47	8.51	15.46
			PI(M36)	76	76	100	95.3	100	66	86.8	77.1	93.5	8.05	5.99	10.83
		18-55y	PRE	33	12	36.4	20.4	54.9	5	15.2	5.1	31.9	0.35	0.22	0.56
			PI(M1)	33	33	100	89.4	100	31	93.9	79.8	99.3	21.85	12.27	38.89
			PI(M12)	33	33	100	89.4	100	31	93.9	79.8	99.3	17.37	9.76	30.92
			PI(M24)	32	30	93.8	79.2	99.2	27	84.4	67.2	94.7	11.99	6.23	23.06
			PI(M36)	34	32	94.1	80.3	99.3	26	76.5	58.8	89.3	8.58	4.59	16.04

ACWY-TT = MenACWY-TT
MenPS = Mencevax ACWY
11-17y = subjects below 18 years of age
18-55y = subjects of 18 years of age and above
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Month 0
PI(M1) = Post-vaccination at Month 1
PI(M12) = Post-vaccination at Year 1
PI(M24) = Post-vaccination at Year 2
PI(M36) = Post-vaccination at Year 3

Assessor's comment: No SmPC changes are proposed by the company. This is agreed.

2. P46 009

MenACWY-TT-030. (eCTD 12)

The applicant hereby submits to the EMA the final report for the above mentioned paediatric study in accordance with Article 46 of Regulation (EC) No 1901/2006. A short critical expert overview has also been provided for MenACWY-TT-030.
The applicant states that the above mentioned study is part of a clinical development program. Study MenACWY-TT-030 is a year 3 follow-up study of the primary study MenACWY-TT-027. The primary phase study MenACWY-TT-027, as well as the follow-up studies after 1 and 2 years (MenACWY-TT-028 and 029 respectively) were submitted as part of the initial MAA for Nimenrix. Further follow-up of the subjects is planned up to 10 years following primary vaccination in MenACWY-TT-027.A variation application consisting of the full relevant data package (i.e containing several studies to update the labelling with available persistence data) is expected to be submitted by the beginning of 2013.
A line listing of the concerned studies was provided in eCTD sequence 11, related to the submission of another paediatric study under Article 46.

The applicant states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product. Background to clinical dataset

Clinical Study Report for Study 108663 (MenACWY-TT-030 EXT: 027 Y3)
Annex 5 to Clinical Study Report 108658 (MenACWY-TT-027)
(Development Phase IIb)

Title of the study: A phase IIb, open, randomized, controlled primary vaccination study to evaluate the non-inferiority and the persistence of the immune response of GSK Biologicals' meningococcal serogroup ACWY conjugate vaccine given intramuscularly versus *Meningitec*™ or *Mencevax*™ ACWY to healthy subjects aged 1 through 10 years of age.
Note: This study has two stages: the vaccination stage 108658 (MenACWY-TT-027) and the long-term persistence stage (MenACWY-TT-028 EXT: 027 Y1 to MenACWY-TT-032 EXT: 027 Y5) with assessments of long-term protection at 1, 2, 3, 4 and 5 years after vaccination. The vaccination stage of the study was reported in the 108658 (MenACWY-TT-027) study report. This study report presents the analysis of the antibody persistence at 3 years after vaccination. It is an annex report (Annex 5) to the 108658 (MenACWY-TT-027) study report.
Study centres: There were eleven study centres in Finland for this study.
Study period:
Study initiation date: 08 Feb 2010
Study completion date: 12 May 2010
Data lock point: 4 April 2011

Objectives:
Primary*:* The primary objectives of the study were evaluated in study 108658 (MenACWY-TT-027) and only the secondary objectives pertaining to the Year 3 visit are presented in this annex report.

Secondary:
Three years after vaccination:
For subjects of two years and above

- To compare the persistence of the immunogenicity of MenACWY-TT conjugate vaccine with that of the licensed *Mencevax ACWY.*

For subjects below two years of age

- To compare the persistence of the immunogenicity of MenACWY-TT conjugate vaccine with that of the licensed *Meningitec.*

For all subjects
To describe Serious Adverse Events (SAEs) related to vaccination and any event related to the lack of vaccine efficacy (i.e. meningococcal disease) from 6 months up to 3 years after vaccination in a retrospective manner.

Study design: This was an open, randomised [3:1], controlled, multi-centre study with 2 parallel groups.

In addition, the enrolment in the vaccination stage of the study, 108658 (MenACWY-TT-027), was performed to ensure the following distribution (2:1:1) of the population across three age strata: subjects aged 1-<2 years, 2-<6 years and 6-<11 years.
In the vaccination stage of the study, 108658 (MenACWY-TT-027), eligible subjects received one dose of the MenACWY-TT conjugate vaccine or one dose of the control vaccine (*Meningitec* for the 1-<2 year age stratum or *Mencevax* ACWY for the 2-<6 year and 6-<11 year age strata). The 108663 (MenACWY-TT-030 EXT: 027 Y3) study consisted of one visit for each subject and a blood sample (5 ml) was collected from subjects in both groups 3 years after vaccination (Visit 6 [Month 36]). The analyses presented here were performed for the two age strata: 1 - < 2 years and 2 - < 11 years of age (i.e. pooled 2-<6 years and 6-<11 years). The vaccines administered and the group names used in the analyses presented in this annex report are as follows

Vaccine treatment*	Age strata	Group name
MenACWY-TT	1–<2 years	ACWY<2
	2–<11 years	ACWY≥2
Meningitec	1–<2 years	MenCCRM
Mencevax ACWY	2–<11 years	MenPS

* Vaccine that was administered in the vaccination phase of the study.

Number of subjects	Total (1-<2 & 2-<11)	1-<2 years age stratum			2-<11 years age stratum		
		ACWY <2	MenCCRM	Total	ACWY ≥2	MenPS	Total
Planned	**608**	228	76	**304**	228	76	**304**
Enrolled & vaccinated in study 108658 (MenACWY-TT-027)	**613**	229	75	**304**	231	78	**309**
Subjects not participating in study 108663 (MenACWY-TT-030 EXT: 027 Y3)	**151**	44	37	**81**	30	40	**70**
Subjects enrolled in study 108663 (MenACWY-TT-030 EXT: 027 Y3): Total Cohort Year 3	**462**	185	38	**223**	201	38	**239**
Immunogenicity ATP cohort for persistence Year 3	**448**	177	37	**214**	197	37	**234**

ACWY<2 = MenACWY-TT (1-<2), MenCCRM = *Meningitec* (1-<2), ATP = According-to-protocol
ACWY≥2 = MenACWY-TT (2-<11), MenPS = *Mencevax* ACWY (2-<11)

Diagnosis and criteria for inclusion: Subjects who satisfied criteria for inclusion in the vaccination stage of the study (see 108658 [MenACWY-TT-027] study report), who were primed with the MenACWY-TT conjugate vaccine or the control vaccine (*Meningitec* for the 1-<2 year age stratum or *Mencevax* ACWY for the 2–<11 year age stratum) in the vaccination stage of the study and who were eligible to enter the persistence study were enrolled. Written informed consent was obtained from the parents or the legally acceptable representative of the subjects at the time of study entry in study 108658 (MenACWY-TT-027). Additional exclusion criteria for the long-term persistence stages of the study were: a history of meningococcal disease due to serogroup A, C, W-135 or Y and vaccination with meningococcal plain polysaccharide vaccine or a meningococcal polysaccharide protein conjugate

Diagnosis and criteria for inclusion:
Subjects who satisfied criteria for inclusion in the vaccination stage of the study (see 108658 [MenACWY-TT-027] study report), who were primed with the MenACWY-TT conjugate vaccine or the control vaccine (*Meningitec* for the 1-<2 year age stratum or *Mencevax* ACWY for the 2–<11 year age stratum) in the vaccination stage of the study and who were eligible to enter the persistence study were enrolled. Written informed consent was obtained from the parents or the legally acceptable representative of the subjects at the time of study entry in study 108658 (MenACWY-TT-027). Additional exclusion criteria for the long-term persistence stages of the study were: a history of meningococcal disease due to serogroup A, C, W-135 or Y and vaccination with meningococcal plain polysaccharide vaccine or a meningococcal polysaccharide protein conjugate vaccine other than the study vaccine. These criteria were to be checked at each long-term time point. If one became applicable at a particular time point, the reason was to be documented and the subject could not enter the long term follow-up for that year and for the subsequent years

Study vaccine, dose, mode of administration, lot no.:

No vaccine was administered during this long-term persistence stage of the study. However, the vaccines that were administered during the vaccination stage of the study 108658 (MenACWY-TT-027) are presented in Table 1.
Vaccination schedule /site:
A single vaccine dose of the MenACWY-TT vaccine or control vaccine was administered at Visit 1 (i.e. at age 1-<2 years, 2-<6 years or 6-<11 years according to the age strata) according to the randomised assignment. The MenACWY-TT vaccine was administered intramuscularly in the deltoid or thigh.
Control vaccines/ site:
Age stratum 1-<2 years: Pfizer's commercially available *Meningitec*; intramuscular administration in the deltoid or thigh.
Age strata 2-<6 years and 6-<11 years: GSK Biologicals' commercially available *Mencevax* ACWY; subcutaneous administration in the upper arm.
All vaccines were administered in the non-dominant side or the left side if the dominant side was not known.

Table 1: Study and reference (control) vaccines administered during the vaccination stage of the study: Formulation, presentations and lot number

Vaccine	Formulation	Presentation (Volume*)	Lot number (diluents lot no)
MenACWY-TT vaccine	5 µg of polysaccharide A (PSA) conjugated to tetanus toxoid (TT), 5 µg of polysaccharide C (PSC) conjugated to TT, 5 µg of polysaccharide W-135 (PSW-135) conjugated to TT, 5 µg of polysaccharide Y (PSY) conjugated to TT.	Lyophilised pellet to be reconstituted with saline diluent (0.5 ml).	DMECA007A (AD02B118A)
GSK Biologicals' meningococcal serogroups ACWY plain polysaccharide vaccine, *Mencevax* ACWY	50 µg PSA, 50 µg PSC, 50 µg PSW-135, 50 µg PSY.	Lyophilised pellet to be reconstituted with saline diluent (0.5 ml).	AMENB045BZ (AD02B118A)
Pfizer's meningococcal C conjugate vaccine, *Meningitec*	10 µg of capsular polysaccharide of meningococcal group C conjugated to 15 µg of *Corynebacterium diphtheria* CRM_{197} protein, Aluminium as salts.	Whitish liquid in vial (0.5 ml).	14838
* volume after reconstitution			

Duration of treatment:
No treatment was administered during study 108663 (MenACWY-TT-030 EXT: 027 Y3).

Criteria for evaluation:
Immunogenicity:
Measurement of antibody titres against meningococcal vaccine antigen components in blood samples obtained at approximately 36 months after vaccination in study 108658 (MenACWY-TT-027) in all subjects:

- Determination of bactericidal antibody titres against *Neisseria meningitidis* serogroups A, C, W- 135 and Y (rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY) using serum bactericidal activity (SBA) assay with rabbit complement (assay cut-off was 1:8).

To support the data obtained by rSBA testing, antibody concentrations against meningococcal polysaccharides were planned to be assessed by Enzyme-linked Immunosorbent Assay (ELISA) at 36 months after vaccination, but the sponsor decided not to perform the ELISA testing for the following reasons:

- the World Health Organisation (WHO) considers SBA the primary means of assessing immune response to meningococcal conjugate vaccines [WHO, 2006; WHO, 1999].
- circulating bactericidal antibodies are more critical for persistent protection against meningococcal disease than non-functional antibodies against meningococcal polysaccharides [CDC, 2011; WHO, 2006].
-

Safety: Recording of SAEs considered related to vaccination by the investigator that occurred from the last study contact (Visit 5/Month 24) up to the Year 3 visit (Visit 6/Month 36).
Note: At the Year 3 visit, subject's parents/guardians were asked, in a retrospective manner, if any SAE had occurred since the Month 24 visit. Only those SAEs that were determined by the investigator to have a causal relationship to the vaccination were recorded. Any event related to the lack of vaccine efficacy during the long-term persistence stage or related to study participation was to be described in detail.

Subject eligibility and exclusion from ATP analyses:
Of the 613 subjects who were enrolled and vaccinated in study 108658 (MenACWY-TT-027); 462 subjects returned for the Year 3 visit (386 MenACWY-TT-primed subjects, 38 *Meningitec*-primed subjects and 38 *Mencevax* ACWY-primed subjects).
Eighty-one subjects 1-<2 years and 70 subjects 2-<11 years did not participate in the Year 3 visit. About half of these subjects within each age stratum did not participate because they had a suboptimal response to meningococcal serogroup C vaccination in at least one of the previous timepoints and received an extra dose of meningococcal serogroup C vaccine before the Year 3 visit. The percentage of subjects not participating because of this reason was 37.3% in the MenCCRM group, 47.4% in the MenPS group, 5.2% in the ACWY<2 group and 1.7% in the ACWY $^{3}2$ group. Because of the imbalance between study groups in the percentage of subjects not participating to this study timepoint, additional analyses were performed to investigate the impact of the subjects who dropped out based on this reason.
1-<2 year stratum: Of the 223 subjects in the Total Cohort Year 3, 9 subjects (8 in the ACWY<2 group, one in the MenCCRM group) were eliminated from the ATP cohort for persistence Year 3. For 4 of these subjects (all in ACWY<2 group), the elimination codes assigned in study 108658 (MenACWY-TT-027) and the Year 1 and Year 2 long term persistence studies 108660 (MenACWY-TT-028 EXT 027 Y1) and 108661 (MenACWY-TT-029 EXT 027 Y2) were still applicable in the current study 108663 (MenACWY-TT-030 EXT 027 Y3). Two subjects in the ACWY<2 group were eliminated due to noncompliance with the blood sampling schedule and 2 subjects in the ACWY<2 group and 1 subject in the MenCCRM group due to essential serological data missing because no blood sample was taken at the Year 3 visit.

2-<11 year stratum: Of the 239 subjects in the Total Cohort Year 3, 5 subjects (4 in the ACWY ≥2 group and 1 in the MenPS group) were eliminated from the ATP cohort for persistence Year 3. For one subject (in MenPS group), the elimination code assigned in study 108658 (MenACWY-TT-027) was still applicable in the current study 108663 (MenACWY-TT-030 EXT 027 Y3). Four subjects in the ACWY ≥2 group were eliminated due to essential serological data missing. No blood sample was taken at the Year 3 visit for 3 subjects and for 1 subject a blood sample was taken, was sent to GSK Biologicals for testing, but was not received by GSK Biologicals.

Demography results
The mean age of the subjects in the ATP cohort for persistence Year 3 was 55.0 months (range 48 to 59 months) for the subjects in the 1-<2 years stratum and 109.4 months (range 59 to 167 months) for subjects in the 2-<11 years stratum. There was a similar proportion of males and females in each group and in each of the age strata. The majority of the subjects in each group and in each of the age strata were White/Caucasian/European heritage (98.1% in the 1-<2 years age stratum and 99.1% in the 2-<11 years age stratum).

Immunogenicity results: The analysis was performed on the ATP cohort for persistence Year 3. As fewer than 5% of the subjects who came back for the Year 3 visit with serological results were excluded from this ATP cohort for both age strata, no additional analysis based on the Total Cohort Year 3 was performed to complement the ATP analysis.

Subjects aged 1-< 2 years
36 months (Year 3) after vaccination (Table 2):

- 90.8% (rSBA-MenC) to 98.9% (rSBA-MenW-135) of the subject in the ACWY<2 group had an rSBA antibody titre ≥1:8 and 97.3% of the subjects in group MenCCRM had an rSBA-MenC antibody titre ≥1:8.
- 50.0% (rSBA-MenC) to 94.7% (rSBA-MenA) of the subjects in the ACWY<2 group had an rSBA antibody titre ≥1:128 and 59.5% of the subjects of group MenCCRM had an rSBA-MenC antibody titre ≥1:128.
- rSBA GMTs in the ACWY<2 group ranged from 125.1 (MenC) to 583.2 (MenY). In the MenCCRM group the rSBA-MenC GMT was 185.7

The exploratory group comparisons suggested:

- no difference between ACWY<2 and MenCCRM groups in terms of subjects with rSBA-MenC antibody titres ≥ 1:8 or ≥ 1:128 since the 95% CI on the group difference included 0.
- no difference between ACWY<2 and MenCCRM groups in terms of rSBA-MenC GMT since the 95% CI on the group ratio included 1.

Refer to Section 'Statistical methods' for the reliability of such analyses.

Table 2: Percentage of subjects with rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs - age stratum 1-<2 years (ATP cohort for persistence Year 3).

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenA	ACWY<2	PRE	151	65	43.0	35.0	51.3	49	32.5	25.1	40.5	23.0	16.4	32.2
		PI(M1)	177	177	100	97.9	100	177	100	97.9	100	3787.4	3353.2	4277.8
		PI(M12)	174	172	98.9	95.9	99.9	170	97.7	94.2	99.4	974.4	831.0	1142.4
		PI(M24)	165	164	99.4	96.7	100	156	94.5	89.9	97.5	575.2	494.0	669.9
		PI(M36)	170	168	98.8	95.8	99.9	161	94.7	90.2	97.6	518.6	447.6	600.8
	MenCCRM	PRE	35	15	42.9	26.3	60.6	12	34.3	19.1	52.2	21.8	10.8	44.1
		PI(M1)	32	10	31.3	16.1	50.0	6	18.8	7.2	36.4	14.4	7.0	29.4
		PI(M12)	22	7	31.8	13.9	54.9	7	31.8	13.9	54.9	17.6	6.5	47.6
		PI(M24)	30	21	70.0	50.6	85.3	18	60.0	40.6	77.3	56.5	28.5	112.2
		PI(M36)	32	27	84.4	67.2	94.7	21	65.6	46.8	81.4	117.1	65.0	211.2
rSBA-MenC	ACWY<2	PRE	163	71	43.6	35.8	51.5	25	15.3	10.2	21.8	15.5	11.9	20.0
		PI(M1)	175	175	100	97.9	100	173	98.9	95.9	99.9	887.0	770.4	1021.2
		PI(M12)	169	169	100	97.8	100	123	72.8	65.4	79.3	223.5	192.2	259.8
		PI(M24)	171	171	100	97.9	100	102	59.6	51.9	67.1	141.2	120.3	165.6
		PI(M36)	174	158	90.8	85.5	94.7	87	50.0	42.3	57.7	125.1	96.7	162.0
	MenCCRM	PRE	34	12	35.3	19.7	53.5	4	11.8	3.3	27.5	12.0	6.9	20.9
		PI(M1)	36	36	100	90.3	100	33	91.7	77.5	98.2	727.6	478.7	1105.8
		PI(M12)	35	35	100	90.0	100	25	71.4	53.7	85.4	218.3	157.9	301.8
		PI(M24)	36	36	100	90.3	100	16	44.4	27.9	61.9	158.6	103.8	242.2
		PI(M36)	37	36	97.3	85.8	99.9	22	59.5	42.1	75.2	185.7	118.3	291.5
rSBA-MenW-135	ACWY<2	PRE	167	50	29.9	23.1	37.5	32	19.2	13.5	26.0	11.7	9.0	15.1
		PI(M1)	177	177	100	97.9	100	177	100	97.9	100	5563.5	4976.9	6219.4
		PI(M12)	176	176	100	97.9	100	173	98.3	95.1	99.6	904.9	792.5	1033.2
		PI(M24)	173	172	99.4	96.8	100	158	91.3	86.1	95.1	439.3	379.0	509.4
		PI(M36)	174	172	98.9	95.9	99.9	151	86.8	80.8	91.4	439.8	370.5	522.0
	MenCCRM	PRE	33	11	33.3	18.0	51.8	7	21.2	9.0	38.9	12.6	6.8	23.5
		PI(M1)	36	14	38.9	23.1	56.5	10	27.8	14.2	45.2	17.5	9.2	33.6
		PI(M12)	35	22	62.9	44.9	78.5	12	34.3	19.1	52.2	37.9	20.1	71.3
		PI(M24)	30	15	50.0	31.3	68.7	7	23.3	9.9	42.3	22.9	11.6	45.1
		PI(M36)	33	24	72.7	54.5	86.7	14	42.4	25.5	60.8	64.5	33.5	124.3
rSBA-MenY	ACWY<2	PRE	166	96	57.8	49.9	65.4	66	39.8	32.3	47.6	37.4	27.4	51.0
		PI(M1)	177	177	100	97.9	100	176	99.4	96.9	100	2875.6	2540.0	3255.6
		PI(M12)	176	175	99.4	96.9	100	169	96.0	92.0	98.4	799.2	683.3	934.7
		PI(M24)	171	168	98.2	95.0	99.6	153	89.5	83.9	93.6	532.8	439.7	645.6
		PI(M36)	177	174	98.3	95.1	99.6	155	87.6	81.8	92.0	583.2	479.0	709.9

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	MenCCRM	PRE	36	24	66.7	49.0	81.4	16	44.4	27.9	61.9	52.5	26.7	103.3
		PI(M1)	36	29	80.6	64.0	91.8	20	55.6	38.1	72.1	101.5	54.3	189.7
		PI(M12)	35	24	68.6	50.7	83.1	19	54.3	36.6	71.2	75.7	36.2	158.3
		PI(M24)	35	27	77.1	59.9	89.6	18	51.4	34.0	68.6	100.6	50.6	200.0
		PI(M36)	36	33	91.7	77.5	98.2	21	58.3	40.8	74.5	176.0	97.6	317.3

ACWY<2 = MenACWY-TT (1-<2)
MenCCRM = *Meningitec* (1-<2)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Month 0
PI (M1) = Post-vaccination at Month 1
PI (M12) = Post-vaccination at Month 12
PI (M24) = Post-vaccination at Month 24
PI (M36) = Post-vaccination at Month 36

Assessor's comment: It is noted that the results for the MenCCRM group are higher at year 3 than year 2 These results are likely to be biased as a higher number of subjects in the control arm dropped-out because of meningococcal serogroup C revaccination.

Subjects aged 2-<11 years

36 months (Year 3) after vaccination (Table 3):

- At least 98.4% (rSBA-MenC) of the subjects in the ACWY≥2 group and 81.1% (rSBA-MenY) to 91.2% (rSBA-MenA) of the subjects in the MenPS group had an rSBA antibody titre ≥1:8.
- 72.9% (rSBA-MenC) to 100% (rSBA-MenY) of the subjects in the ACWY≥2 group and 51.4% (rSBA-MenY) to 79.4% (rSBA-MenA) of the subjects in the MenPS group had an rSBA antibody titre ≥1:128.
- rSBA GMTs ranged from 244.3 (MenC) to 1737.1 (MenW-135) in the ACWY≥2 group and from 103.8 (MenY) to 218.8 (MenA) in group MenPS.

The exploratory group comparisons suggested:

- a higher percentage of subjects with rSBA-MenA antibody titres ≥1:8 and ≥1:128, rSBA-MenC antibody titres ≥1:8, rSBA-MenW-135 antibody titres ≥1:8 and ≥1:128 and rSBA-MenY antibody titres ≥1:8 and 1:128 in group ACWY≥2 than in group MenPS since the LL of the 95% CI on the group difference was above 0.
- a higher rSBA-MenA, rSBA-MenW-135 and rSBA-MenY GMT in group ACWY≥2 than in group MenPS since the 95% CI on the GMT ratio was above 1.

Refer to Section 'Statistical methods' for the reliability of such analyses.

Table 3: Percentage of subjects with rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs - age stratum 2-<11 years (ATP cohort for persistence Year 3).

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenA	ACWY≥2	PRE	162	109	67.3	59.5	74.4	84	51.9	43.9	59.8	58.4	42.8	79.6
		PI(M1)	196	196	100	98.1	100	195	99.5	97.2	100	7513.7	6740.4	8375.7
		PI(M12)	196	195	99.5	97.2	100	195	99.5	97.2	100	2533.4	2211.6	2902.1
		PI(M24)	193	193	100	98.1	100	191	99.0	96.3	99.9	1352.7	1191.4	1535.7
		PI(M36)	192	192	100	98.1	100	190	99.0	96.3	99.9	1184.2	1054.2	1330.3
	MenPS	PRE	31	20	64.5	45.4	80.8	19	61.3	42.2	78.2	69.8	30.6	158.8
		PI(M1)	37	37	100	90.5	100	37	100	90.5	100	2244.3	1737.7	2898.6
		PI(M12)	36	34	94.4	81.3	99.3	32	88.9	73.9	96.9	576.2	334.8	991.7
		PI(M24)	35	33	94.3	80.8	99.3	28	80.0	63.1	91.6	240.1	149.5	385.7
		PI(M36)	34	31	91.2	76.3	98.1	27	79.4	62.1	91.3	218.8	128.9	371.5
rSBA-MenC	ACWY≥2	PRE	184	118	64.1	56.7	71.1	55	29.9	23.4	37.1	36.5	27.8	48.0
		PI(M1)	196	196	100	98.1	100	195	99.5	97.2	100	2524.9	2162.1	2948.5
		PI(M12)	195	195	100	98.1	100	178	91.3	86.4	94.8	509.4	439.4	590.6
		PI(M24)	195	195	100	98.1	100	150	76.9	70.4	82.6	273.1	229.3	325.1
		PI(M36)	192	189	98.4	95.5	99.7	140	72.9	66.0	79.1	244.3	200.8	297.3
	MenPS	PRE	35	26	74.3	56.7	87.5	18	51.4	34.0	68.6	61.3	31.4	119.7
		PI(M1)	37	37	100	90.5	100	37	100	90.5	100	1433.7	939.4	2188.0
		PI(M12)	34	34	100	89.7	100	29	85.3	68.9	95.0	437.6	282.9	676.8
		PI(M24)	37	37	100	90.5	100	25	67.6	50.2	82.0	237.9	144.0	393.0
		PI(M36)	37	31	83.8	68.0	93.8	25	67.6	50.2	82.0	163.5	83.8	319.2
rSBA-MenW-135	ACWY≥2	PRE	173	107	61.8	54.2	69.1	81	46.8	39.2	54.5	45.4	33.5	61.5
		PI(M1)	196	196	100	98.1	100	196	100	98.1	100	12158.8	10949.9	13501.1
		PI(M12)	196	196	100	98.1	100	194	99.0	96.4	99.9	3064.7	2692.8	3488.0
		PI(M24)	195	194	99.5	97.2	100	193	99.0	96.3	99.9	1324.4	1154.4	1519.4
		PI(M36)	196	196	100	98.1	100	192	98.0	94.9	99.4	1737.1	1503.8	2006.7
	MenPS	PRE	33	22	66.7	48.2	82.0	14	42.4	25.5	60.8	57.4	27.6	119.4
		PI(M1)	37	37	100	90.5	100	37	100	90.5	100	2602.6	1795.6	3772.4
		PI(M12)	37	37	100	90.5	100	36	97.3	85.8	99.9	587.0	411.3	837.9
		PI(M24)	34	30	88.2	72.5	96.7	25	73.5	55.6	87.1	182.8	104.0	321.2
		PI(M36)	35	29	82.9	66.4	93.4	21	60.0	42.1	76.1	112.9	59.9	212.6
rSBA-MenY	ACWY≥2	PRE	192	127	66.1	59.0	72.8	85	44.3	37.1	51.6	55.4	41.3	74.3
		PI(M1)	196	196	100	98.1	100	195	99.5	97.2	100	6655.7	6009.1	7372.0
		PI(M12)	196	196	100	98.1	100	195	99.5	97.2	100	2164.0	1924.2	2433.6
		PI(M24)	195	195	100	98.1	100	194	99.5	97.2	100	1556.4	1355.9	1786.6
		PI(M36)	195	195	100	98.1	100	195	100	98.1	100	1551.6	1381.2	1743.1
	MenPS	PRE	34	19	55.9	37.9	72.8	14	41.2	24.6	59.3	37.2	17.3	80.4
		PI(M1)	37	37	100	90.5	100	37	100	90.5	100	1813.8	1235.6	2662.5
		PI(M12)	34	32	94.1	80.3	99.3	28	82.4	65.5	93.2	467.5	261.3	836.5
		PI(M24)	37	30	81.1	64.8	92.0	20	54.1	36.9	70.5	116.2	59.3	227.7
		PI(M36)	37	30	81.1	64.8	92.0	19	51.4	34.4	68.1	103.8	54.3	198.3

ACWY≥2 = MenACWY-TT (2-<11)
MenPS = *Mencevax* ACWY (2-<11)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Month 0
PI (M1) = Post-vaccination at Month 1
PI (M12) = Post-vaccination at Month 12
PI (M24) = Post-vaccination at Month 24
PI (M36) = Post-vaccination at Month 36

Robustness modelling

The robustness analysis models provided estimated GMTs for rSBA-MenA, rSBA-MenW-135 and rSBA-MenY for groups ACWY<2, ACWY≥2 and MenPS and for rSBA-MenC in groups ACWY<2 and ACWY≥2 that were within 2 fold of the observed values. This indicates that the initial analysis performed at each timepoint separately (i.e. in each study) is not unduly affected by subjects who dropped out.

For rSBA-MenC in the MenCCRM and MenPS groups, the models predicted lower GMTs than the values observed at Year 3. This indicates that the observed rSBA-MenC GMTs at Year 3 are biased by the fact that a higher percentage of subjects in these groups were excluded from the analysis at this timepoint because of a suboptimal response to meningococcal serogroup C vaccination at a previous persistence timepoint.

Safety /reactogenicity:

No SAEs considered related to vaccination or events related to the lack of vaccine efficacy were reported in the period between the Month 6 visit (6 months after vaccination) and the Year 3 visit (36 months after vaccination).
An event of viral meningitis has been reported although this event is not vaccine related nor a case of lack of vaccine efficacy.

MAH Conclusion(s):

This study evaluated antibody persistence at Year 3 (approximately 36 months) after vaccination with one dose of the MenACWY-TT conjugate vaccine or one dose of a control vaccine (*Meningitec* or *Mencevax* ACWY according to age strata in the 108658 [MenACWY-TT-027] study).
Three years 3 after vaccination:

- 90.8% to 98.9% of the subject in the ACWY<2 group had an rSBA antibody titre ≥1:8 and 97.3% of the subjects in group MenCCRM had an rSBA-MenC antibody titre ≥1:8.
- At least 98.4% of the subjects in the ACWY≥2 group and 81.1% to 91.2% of the subjects in the MenPS group had an rSBA antibody titre ≥1:8.
- No SAEs assessed by the investigator as related to vaccination or any events related to the lack of vaccine efficacy were reported up to 3 years after vaccination.

Note that these results are likely biased. At Year 3 a higher percentage of the subjects receiving a control vaccine than the subjects receiving MenACWY-TT dropped out because of meningococcal serogroup C revaccination. The model showed that the observed rSBA-MenC values may be overestimated. No confirmatory analyses were performed on secondary objectives.

MenACWY-TT-030. (eCTD 12)
Annex Report 6 (hSBA data)

Annex report 6 provides hSBA results for 1 to 2 year age group for both Year 2 and Year 3 persistence time points. The conclusions are provided below.

This study evaluated the antibody persistence using serum bactericidal activity assay with human complement at Year 2 and Year 3 after vaccination with one dose of MenACWY-TT conjugate vaccine or one dose of a control vaccine (*Meningitec*) in subjects of age strata 1-<2 years.

Two years after vaccination:

Overall, at least 90.8% of the subjects vaccinated with MenACWY-TT had hSBA titres ≥1:4 and ≥1:8 against serogroups C, W-135 and Y. 40.6% and 36.1% had hSBA-MenA titres ≥1:4 and ≥1:8, respectively. In the MenCCRM group, which had only received a MenC conjugate vaccine, 54.9% of subjects had hSBA-MenC titres ≥1:4 and ≥1:8.

Three years after vaccination:

Overall, at least 73.6% of the subjects vaccinated with MenACWY-TT had hSBA titres ≥1:4 and ≥1:8 against serogroups C, W-135 and Y. 21.8% and 17.6% had hSBA-MenA titres ≥1:4 and ≥1:8, respectively. In the MenCCRM group which had only received a MenC conjugate vaccine, 75.8% of subjects had hSBA-MenC titres ≥1:4 and ≥1:8.

Note that these Year 3 results are likely biased due to differential subject drop-out between the two
treatment groups. As shown in Annex Report 5 (108663 [MenACWY-TT-030 EXT: 027 Y3]) for rSBAMenC, at Year 3 a higher percentage of the subjects receiving a control vaccine than the

subjects receiving MenACWY-TT dropped out because of meningococcal serogroup C revaccination after suboptimal response to meningococcal serogroup C vaccination in at least one of the previous timepoints. The percentage of subjects not participating because of this reason was 37.3% in the MenCCRM group and 5.2% in the ACWY<2 group. The data modeling performed for rSBA-MenC indicated that the rSBA GMT value of the control group may be overestimated. No confirmatory analyses were performed on secondary objectives.
No SAEs assessed by the investigator as related to vaccination or any events related to the lack of vaccine efficacy were reported up to 3 years after vaccination.

Assessor's comments: The Company conclude that 3 year persistence data do not require amendment to the SmPC and this is agreed.

3. P46 014
MenACWY-TT-031 EXT: 027 Y4 (eCTD seq 19)

Study MenACWY-TT-031 is a year 4 follow-up study of the primary study MenACWY-TT-027. The primary phase study MenACWY-TT-027, as well as the follow-up studies after 1 and 2 years (MenACWY-TT-028 and 029 respectively) were submitted as part of the initial MAA for Nimenrix. The follow-up study after 3 years (MenACWY-TT-030)is discussed above (P46 009).
Further follow-up of the subjects is planned up to 10 years following primary vaccination in MenACWY-TT-027. A variation application consisting of the full relevant data package (i.e containing several studies to update the labelling with available persistence data) is expected to be submitted by the beginning of 2013.

The applicant states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product.
No SmPC and PL changes are proposed.

Study No.: 108665 (MenACWY-TT-031 EXT: 027 Y4)
Title of the study: A phase IIb, open, randomized, controlled primary vaccination study to evaluate the non-inferiority and the persistence of the immune response of GSK Biologicals' meningococcal serogroup ACWY conjugate vaccine given intramuscularly versus *Meningitec*™ or *Mencevax*™ ACWY to healthy subjects aged one through ten years of age.

Objectives
Primary:
One month after vaccination:
The primary objectives of the study were evaluated in study 108658 (MenACWY-TT-027) and only the secondary objectives pertaining to the Year 4 visit are presented in this annex report.

Secondary:
Four years after vaccination:
For subjects of two years of age and above
- To compare the persistence of the immunogenicity of MenACWY-TT conjugate vaccine with that of the licensed *Mencevax* ACWY.

For subjects below two years of age
- To compare the persistence of the immunogenicity of MenACWY-TT conjugate vaccine with that of the licensed *Meningitec*.

For all subjects
- To describe Serious Adverse Events (SAEs) related to vaccination and any event related to the lack of vaccine efficacy (i.e. meningococcal disease) from six months up to four years after vaccination in a retrospective manner.

Study design:
This was an open, randomized [3:1], controlled, multi-center study with two parallel groups. In addition, the enrollment in the vaccination stage of the study, 108658 (MenACWY-TT-027), was performed to ensure the following distribution (2:1:1) of the population across three age strata: subjects aged 1-<2 years, 2-<6 years and 6-<11 years. In the vaccination stage of the study, eligible subjects received one dose of the MenACWY-TT conjugate vaccine or one dose of the control vaccine (*Meningitec* for the 1-<2 year age stratum or *Mencevax* ACWY for the 2-<6 year and 6-<11 year age strata). The 108665 (MenACWY-TT-031 EXT: 027 Y4) persistence stage consisted of one visit for each subject and a blood sample (5 mL) was collected from subjects in both groups four years after vaccination (Visit 7 [Year 4]). The vaccines administered and the group names used were as follows:

Vaccine treatment*	Age strata	Group name
MenACWY-TT	1–<2 years	ACWY<2
	2–<11 years	ACWY≥2
Meningitec	1–<2 years	MenCCRM
Mencevax ACWY	2–<11 years	MenPS
* Vaccine that was administered in the vaccination phase of the study.		

- Vaccine that was administered in the vaccination phase of the study.

Study vaccine, dose, mode of administration, lot no.:
No vaccine was administered during this long-term persistence stage of the study.

Study population:
Subjects who satisfied the criteria for inclusion in the vaccination stage of the study (see 108658 [MenACWY-TT-027] study report), who were primed with the MenACWY-TT conjugate vaccine or the control vaccine (*Meningitec* for the 1-<2 year age stratum or *Mencevax* ACWY for the 2–<11 year age stratum) in the vaccination stage of the study and who were eligible to enter the persistence stage were enrolled. Written informed consent was obtained from the parents or the legally acceptable representative of the subjects at the time of study entry in study 108658 (MenACWY-TT-027). Additional exclusion criteria for the long-term persistence stages of the study to be checked at each long-term time point were: a history of meningococcal disease due to serogroup A, C, W-135 or Y and vaccination with meningococcal plain polysaccharide vaccine or a meningococcal polysaccharide protein conjugate vaccine other than the study vaccine. If one became applicable at a particular time point, the reason was to be documented and the subject could not enter the long-term follow-up for that year and for the subsequent years.

Statistical methods:
Statistical analyses were performed as per protocol or reporting and analysis plan (RAP). Only the statistical methods pertaining to this Year 4 persistence stage are presented in this annex report. Analyses were performed for the 1-<2 years and the 2-<11 years age strata.

Demography:
Demographic characteristics (age in months, gender, race) of each study cohort were tabulated per group.
The mean age (in months) (with the range and standard deviation) as a whole and per group was calculated
The distribution of subjects enrolled among the study centers was tabulated as a whole and per group.

Primary Outcome/Efficacy Variable:
The primary outcome of the study was evaluated in study 108658 (MenACWY-TT-027) and only the secondary outcomes pertaining to the Year 4 visit are presented in this annex report.

Secondary Outcome/Efficacy Variable(s):
Immunogenicity - Persistence:
Measurement of antibody titers against meningococcal vaccine antigen components in blood samples obtained at approximately four years after vaccination in study 108658 (MenACWY-TT-027) in all evaluable subjects:

- Determination of bactericidal antibody titers against *Neisseria meningitidis* serogroups A, C, W-135 and Y (rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY) using serum bactericidal activity assay with rabbit complement (rSBA) (assay cut-off was 1:8). Measurement of antibody titers against meningococcal vaccine antigen components in blood samples obtained at approximately four years after vaccination in study 108658 (MenACWY-TT-027) in subjects below two years of age:

- Determination of bactericidal antibody titers against *Neisseria meningitidis* serogroups A, C, W-135 and Y (hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY) using serum bactericidal activity assay with human complement (hSBA) (assay cut-off was 1:4).

Safety:

- Occurrence of SAEs related to vaccination and any event related to lack of vaccine efficacy (i.e. meningococcal disease) that occurred from Month 6 up to the Year 4 visit (Visit 7). Note: At the Year 4 visit, subject's parents/guardians were asked, in a retrospective manner, if any SAE had occurred since the Year 3 visit. Only those SAEs that were determined by the investigator to have a causal relationship to the vaccination were recorded. Any event related to the lack of vaccine efficacy during the long-term persistence stage or related to study participation were to be described in detail.

Immunogenicity - Persistence:

The analysis of antibody persistence was based on the according-to-protocol (ATP) cohort for antibody persistence at Year 4. The percentage of subjects who came back for the Year 4 follow-up with serological results excluded from the ATP cohort was higher than 5%, therefore a second analysis based on the Total Cohort at Year 4 was performed to complement the ATP analysis.
Serological assays were performed at the GSK Biologicals' central laboratory (for rSBA and hSBA) and at the Health Protection Agency (HPA) (only for rSBA). As these were different tests, the results were presented separately.

Within-group analysis

Four years after vaccination, for each vaccine group and for all age strata, for rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY, and for subjects below two years of age for hSBAMenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY:

- Geometric Mean Titers (GMTs) with 95% CIs were calculated.
- Percentages of subjects with antibody titers above the proposed endpoint cut-offs with exact 95% confidence intervals (CIs) were calculated.
- The distribution of antibody titers was tabulated.
- Antibody titers were also presented using reverse cumulative curves (RCCs).

Between-group analysis

The comparability of the MenACWY-TT vaccine versus the control vaccine in terms of persistence of antibodies to different antigens at Year 4 in all subjects was analyzed through:

- Computation of the asymptotic standardized 95% CI on the difference in the percentage of subjects with rSBA ≥1:8 and ≥1:16 (only for subjects below 2 years of age) between the study vaccine group and (minus) the study control group for each of the four serogroups.
- Computation of the 95% CIs of the GMT ratios between the study vaccine group and (over) the control vaccine group. This was performed using an Analysis of Covariance (ANCOVA) model on the logarithm10 transformation of the titers using the pre-vaccination logarithm$_{10}$ transformation of the titers, the age strata and the vaccine group as covariates.

Exploratory between-group comparisons were examined as follows: the exclusion of 1 from the 95% CI on the GMT ratios or 0% from the 95% CI on the differences in percentage of subjects with titers above proposed cut-offs was used to highlight potential group differences. However, these potential differences should be interpreted with caution considering that there was no adjustment for multiplicity for these comparisons and that the clinical relevance of any differences was not accounted for in the planning of the exploratory analyses.

Analysis of Safety:

The number of subjects who experienced SAEs related to vaccination from 6 months up to four years after vaccination in a retrospective manner was to be reported in detail.

Study population (Total Cohort Year 4)		
Synopsis Table 1: Age stratum 1-<2 years		
Number of subjects	**ACWY<2**	**MenCCRM**
Planned, N	228	76
Randomized, N (Total Cohort Year 4)	165	34
Completed, n (%)	165 (100)	34 (100)
Demographics	**ACWY<2**	**MenCCRM**
N (Total Cohort Year 4)	165	34
Females:Males	89:76	17:17
Mean Age, months (SD)	67.0 (3.14)	67.3 (3.50)
White - Caucasian / European heritage, n (%)	163 (98.8)	33 (97.1)
ACWY<2 = MenACWY-TT (1-<2) MenCCRM = *Meningitec* (1-<2)		
Synopsis Table 2: Age stratum 2-<11 years		
Number of subjects	**ACWY≥2**	**MenPS**
Planned, N	228	76
Randomized, N (Total Cohort Year 4)	192	32
Completed, n (%)	192 (100)	32 (100)
Demographics	**ACWY≥2**	**MenPS**
N (Total Cohort Year 4)	192	32
Females:Males	99:93	17:15
Mean Age, months (SD)	119.9 (30.68)	128.0 (26.96)
White - Caucasian / European heritage, n (%)	190 (99.0)	32 (100)
ACWY≥2 = MenACWY-TT (2-<11) MenPS = *Mencevax* ACWY (2-<11)		

MAH Summary:
Subject eligibility and exclusion from ATP analyses:
Of the 613 subjects who were enrolled and vaccinated in study 108658 (MenAXWY-TT-027), 423 subjects returned for the Year 4 visit (357 MenACWY-TT-primed subjects, 34 Meningitec-primed subjects and 32 Mencevax ACWY-primed subjects).
A total of 105 aged subjects 1-<2 years and 85 subjects aged 2-<11 years did not participate in the Year 4 visit. About half of these subjects within each age stratum did not participate because they had a suboptimal response to meningococcal serogroup C vaccination on at least one of the previous time points and/or received an extra dose of meningococcal serogroup C vaccine before the Year 4 visit. The percentage of subjects not participating because of this reason was 38.7% in the MenCCRM group, 51.3% in the MenPS group, 10.5% in the ACWY<2 group and 3.0% in the ACWY≥2 group. Because of the imbalance between study groups in the percentage of subjects not participating to this study time point, the study results are likely biased.

Subjects aged 1-<2 years
Of the 199 subjects in the Total Cohort Year 4, 16 subjects (13 in the ACWY<2 group and three in the MenCCRM group) were eliminated from the ATP cohort for persistence Year 4. For four of these subjects (all in the ACWY<2 group), the elimination codes assigned in study 108658 (MenACWY-TT-027) and the Year 1, 2 and 3 long-term persistence studies were still applicable in the current study 108665 (MenACWY-TT-031 EXT 027 Y4). Eight subjects (five in the ACWY<2 group and three in the MenCCRM group) were eliminated due to non-compliance with the blood sampling schedule, three subjects in the ACWY<2 group due to essential serological data missing (no blood sample was taken at the Year 4 visit) and one subject in the ACWY<2 group due to administration of medication forbidden by the protocol (gamma-globulin).

Subjects aged 2-<11 years
Of the 224 subjects in the Total Cohort Year 4, seven subjects (four in the ACWY≥2 group and three in the MenPS group) were eliminated from the ATP cohort for persistence Year 4. For one subject (in the MenPS group), the elimination code assigned in study 108658 (MenACWY-TT-027) was still applicable in the current study 108665 (MenACWY-TT-031 EXT 027 Y4). Six subjects (four in the ACW≥2 group and two in the MenPS group) were eliminated due to non-compliance with the blood sampling schedule.

Demography:
The mean age of the subjects in the ATP cohort for persistence Year 4 was 67.0 months (range 59 to 72 months) for the subjects in the 1-<2 years stratum and 121.1 months (range 72 to 180 months) for subjects in the 2-<11 years stratum. There was a comparable proportion of males and females in each group and in each of the age strata. The majority of the subjects in each group and in each of the age strata were of White - Caucasian/European heritage (98.4% in the 1-<2 years age stratum and 99.1% in the 2-<11 years age stratum).

Immunogenicity - Persistence:
Immunogenicity analysis was performed on the ATP cohort for persistence Year 4. As more than 5% of the subjects who came back for the Year 4 visit with serological results were excluded from this ATP cohort for both age strata, a second analysis based on the Total Cohort Year 4 was performed to complement the ATP analysis.

Measured at GSK
Subjects aged 1-<2 years

- Four years after vaccination: 90.7% to 97.8% (rSBA-MenA) of the subjects in the ACWY<2 group had an rSBA antibody titer ≥ 1:8 and 90.0% of the subjects in the MenCCRM group had an rSBA-MenC antibody titer ≥ 1:8.
- 51.1% (rSBA-MenC) to 94.1% (rSBA-MenA) of the subjects in the ACWY<2 group had an rSBA antibody titer ≥ 1:128 and 46.7% of the subjects in the MenCCRM group had an rSBA-MenC antibody titer ≥ 1:128
- rSBA GMTs in the ACWY<2 group ranged from 141.9 (rSBA-MenC) to 623.9 (rSBA-MenA). In the MenCCRM group, the rSBA-MenC GMT was 150.5.
- 40.7% (hSBA-MenA) to 85.7% (hSBA-MenC) of the subjects in the ACWY<2 group had an hSBA antibody titer ≥ 1:4 and 77.4% of the subjects in the MenCCRM group had an hSBA-MenC antibody titer ≥ 1:4.
- 39.3% (hSBA-MenA) to 85.7% (hSBA-MenC) of the subjects in the ACWY<2 group had an hSBA antibody titer ≥ 1:8 and 77.4% of the subjects in the MenCCRM group had an hSBA-MenC antibody titer ≥ 1:8.
- hSBA GMTs in the ACWY<2 group ranged from 6.0 (hSBA-MenA) to 51.4 (hSBA-MenC). In the MenCCRM group, the hSBA-MenC GMT was 32.4.

The exploratory group comparisons did not support a difference between the ACWY<2 and MenCCRM groups:

- in terms of subjects with rSBA-MenC antibody titers ≥ 1:8 or ≥ 1:128 and hSBA-MenC antibody titers ≥ 1:4 or ≥ 1:8 since the 95% CIs on the group difference included 0.
- in terms of subjects with rSBA-MenC GMTs and hSBA-MenC GMTs since the 95% CI on the group ratio included 1.

Subjects aged 2-<11 years
Four years after vaccination:

- At least 96.8% (rSBA-MenC) of the subjects in the ACWY≥2 group and 75.9% (rSBAMenW- 135) to 89.7% (rSBA-MenC) of the subjects in the MenPS group had an rSBA antibody titer ≥ 1:8.
- 64.4% (rSBA-MenC) to 100% (rSBA-MenY) of the subjects in the ACWY≥2 group and 51.7% (rSBA-MenY) to 69.0% (rSBA-MenC) of the subjects in the MenPS group had an rSBA antibody titer ≥ 1:128.
- rSBA GMTs ranged from 203.6 (rSBA-MenC) to 1932.3 (rSBA-MenA) in the ACWY≥2 group and from 93.4 (rSBA-MenW-135) to 211.9 (rSBA-MenC) in the MenPS group.

The exploratory group comparisons suggested:

- a higher percentage of subjects with rSBA antibody titers ≥ 1:8 or ≥ 1:128 for serogroups A, W-135 and Y in the ACWY≥2 group than in the MenPS group since the LL of the 95% CI on the group differences were above 0.
- higher rSBA GMTs for serogroups A, W-135 and Y in the ACWY≥2 group than in the MenPS group since the 95% CI on the GMT ratios were above 1.

Measured at HPA
Subjects aged 1-<2 years
Four years after vaccination:

- 30.3% (rSBA-MenC) to 61.2% (rSBA-MenA) of the subjects in the ACWY<2 group had an rSBA antibody titer ≥ 1:8 and 25.8% of the subjects in the MenCCRM group had an rSBA-MenC antibody titer ≥ 1:8.
- 14.5% (rSBA-MenC) to 39.5% (rSBA-MenW-135) of the subjects in the ACWY<2 group had an rSBA antibody titer ≥ 1:128 and 19.4% of the subjects in the MenCCRM group had an rSBA-MenC antibody titer ≥ 1:128.
- rSBA GMTs ranged from 11.2 (rSBA-MenC) to 31.3 (rSBA-MenW-135) in the ACWY<2 group. In the MenCCRM group, the rSBA-MenC GMT was 11.4.

The exploratory group comparisons did not support a difference between the ACWY<2 and MenCCRM groups:

- in terms of subjects with rSBA-MenC antibody titers ≥ 1:8 or ≥ 1:128 since the 95% CIs on the group difference included 0.
- in terms of subjects with rSBA-MenC GMTs since the 95% CI on the group ratio included 1.

Subjects aged 2-<11 years
Four years after vaccination:

- 50% (rSBA-MenC) to 90.4% (rSBA-MenW-135) of the subjects in the ACWY≥2 group and 6.9% (rSBA-MenY) to 41.4% (rSBA-MenC) of the subjects in the MenPS group had an rSBA antibody titer ≥ 1:8.
- 27.7% (rSBA-MenC) to 89.3% (rSBA-MenW-135) of the subjects in the ACWY≥2 group and 3.4% (rSBA-MenY) to 31.0% (rSBA-MenC) of the subjects in the MenPS group had an rSBA antibody titer ≥ 1:128.
- rSBA-GMTs ranged from 21.7 (rSBA-MenC) to 671.1 (rSBA-MenW-135) in the AWCY≥2 group and from 4.7 (rSBA-MenY) to 23.5 (rSBA-MenC) in the MenPS group.

The exploratory group comparisons suggested:

- a higher percentage of subjects with rSBA antibody titers ≥ 1:8 and ≥ 1:128 for serogroups A, W-135 and Y in the ACWY≥2 group than in the MenPS group since the LL of the 95% CI on the group differences were above 0.
- higher rSBA GMTs for serogroups A, W-135 and Y in the ACWY≥2 group than in the MenPS group since the 95% CI on the GMT ratios were above 1.

Assessor's comment: The results for the HPA rSBA are lower than the GSK rSBA data.

Safety /reactogenicity:
No SAEs considered to be possibly related to vaccination by the investigator or considered related to study participation nor events related to the lack of vaccine efficacy were reported from six months up to four years after vaccination.

MAH Conclusion:
This study evaluated antibody persistence at Year 4 (approximately 48 months) after vaccination with one dose of the MenACWY-TT conjugate vaccine or one dose of a control vaccine (*Meningitec* or *Mencevax* ACWY according to age strata in the 108658 [MenACWY-TT-027] study).

Subjects aged 1-<2 years:

- 91.2% to 97.8% of the subjects in the ACWY<2 group had rSBA antibody titers ≥ 1:8 for all 4 serogroups and 90.0% of the subjects in the MenCCRM group had an rSBA-MenC antibody titer ≥ 1:8, when measured at GSK' laboratory.
- □30.3% to 61.2% of the subjects in the ACWY<2 group had rSBA antibody titers □1:8 for all4 serogroups and 25.8% of the subjects in the MenCCRM group had an rSBA-MenC antibody titer ≥ 1:8, when measured at HPA.
- At least 77.5% of subjects in the ACWY<2 group had hSBA titers ≥ 1:4 and ≥ 1:8 against serogroups C, W-135 and Y. 40.7% and 39.3% of the subjects had hSBA-MenA titers ≥ 1:4 and ≥ 1:8, respectively. In the MenCCRM group 77.4% of the subjects had hSBA-MenC titers ≥ 1:4 and ≥ 1:8.

Subjects aged 2-<11 years:

- At least 96.8% of the subjects in the ACWY≥2 group and 75.9% to 89.7% of subjects in the MenPS group had rSBA antibody titers ≥ 1:8 for all 4 serogroups, when measured at GSK.
- 50.0% to 90.4% of the subjects in the ACWY<2 group and 6.9% to 41.4% in the MenPS group had rSBA antibody titers ≥ 1:8 for all 4 serogroups, when measured at HPA.

Note that these results are likely biased. At Year 4, a higher percentage of subjects receiving a control vaccine than subjects receiving MenACWY-TT dropped out because of meningococcal serogroup C revaccination.
No unsolicited AEs were collected during the Year 4 persistence phase of the study.
No SAEs considered to be possibly related to vaccination by the investigator or considered related to study participation nor events related to the lack of vaccine efficacy were reported from six months up to four years after vaccination.

Assessor's comment: The overall conclusions of the MAH are agreed. At present the MAH are collecting persistence data from phase II and phase III studies in adolescents, children and toddlers and these are expected to become available by the end of 2012. The MAH will then submit the more substantial data-set for a type II variation in 2013.

4. □P46 010

MenACWY-TT-048 EXT 039 Y3. (eCTD 13)

The applicant hereby submits to the EMA the final report for MenACWY-TT-048 EXT 039 Y3 paediatric study in accordance with Article 46 of Regulation (EC) No 1901/2006. A short critical expert overview has also been provided.
The applicant states that the above mentioned study is part of a clinical development program. Study MenACWY-TT-048 EXT 039 Y3 is a year 3 follow-up study of the primary study MenACWY-TT-039. The primary phase study MenACWY-TT-039, as well as the follow-up study after 2 years (MenACWY-TT-048 EXT 039 Y2) were submitted as part of the initial MAA for Nimenrix. Further follow-up of the subjects is planned up to 10 years following primary vaccination in MenACWY-TT-039. A variation application consisting of the full relevant data package (i.e containing several studies to update the labelling with available persistence data) is expected to be submitted by the beginning of 2013.

Study title

112036 (MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5)
Annex Report (Y3) Final
Persistence of antibodies after GlaxoSmithKline (GSK) Biologicals' meningococcal vaccine GSK134612 in toddlers.

Study detailed title

A phase III, open, multi-centre, controlled study to evaluate the long-term antibody persistence at 2 years, 3 years and 4 years after a single dose of GSK Biologicals' meningococcal serogroup A, C, W-135, Y- tetanus toxoid conjugate (MenACWY-TT) vaccine versus one dose of *Meningitec*™ administered in healthy 12 through 23-month old children who were primed in study MenACWY-TT-039 (109670) and to evaluate the immunogenicity and safety of a booster dose of the same meningococcal conjugate vaccine as given in the primary study, 4 years after priming.

Study Centres: This study was conducted at 14 centres in Finland.
Study initiation date (Year 3): 24 February 2010
Study completion date (Year 3): 16 November 2010
Data lock point (Date of database freeze): 16 December 2011
Phase: III

Indication: Active immunisation of individuals from the age of 12 to 23 months and above against invasive meningococcal disease caused by *Neisseria meningitidis* group A, C, W-135 and Y.

Treatment:

The subjects were enrolled in this long-term follow-up study MenACWY-TT-048 (112036) using the same randomization scheme as in the primary vaccination study MenACWY-TT-039 (109670) and were allocated with a [3:1] ratio in the following groups:

- ACWY-TT group (N=744 at most): consisting of subjects from both groups (MenACWYTT+ MMRV and MenACWY-TT groups) vaccinated with MenACWY-TT in study MenACWYTT- 039 (109670).
- MenCCRM group (N=248 at most): consisting of subjects from both groups (MMRV and *Meningitec* groups) vaccinated with *Meningitec* in study MenACWY-TT-039 (109670).

All subjects will be boosted at Month 48 (4 years after primary vaccination) with the same meningococcal vaccine as given in the primary study.

Objectives:

Only the objectives pertaining to this Year 3 persistence study are presented in this annex report.

Primary: *Immunogenicity - Persistence*

At 36 months after primary vaccination of toddlers with MenACWY-TT or *Meningitec:*

- To evaluate the persistence of meningococcal antibodies in terms of the percentage of subjects with serum bactericidal activity assay with rabbit complement (rSBA) antibody titres ≥ 1:8 for each of the four serogroups.

Secondary: *Immunogenicity - Persistence :*

At 36 months after primary vaccination with a meningococcal conjugate vaccine:

- To evaluate the persistence of meningococcal A, C, W-135 and Y antibodies in terms of rSBA, serum bactericidal assay activity with human complement (hSBA) and anti-meningococcal polysaccharide (PS) antibodies for each of the four serogroups.

Study design:
Phase III, open, multi-centre and controlled study with 2 parallel groups.
A blood sample was taken 36 months after primary vaccination in study MenACWY-TT-039 (109670).

Study Population:
Healthy male or female subjects having completed the primary study MenACWY-TT-039 (109670) and who were primed with MenACWY-TT or *Meningitec* vaccines, free of obvious health problems (including immunosuppressive or immunodeficient condition or bleeding disorders) as established by medical history and clinical examination before entering into the study, without a history of meningococcal disease, who had not received a meningococcal polysaccharide or a meningococcal polysaccharide conjugate vaccine outside of study MenACWY-TT-039 (109670) or who had not received immunoglobulins and/or blood products within three months of study entry or another clinical study drug within 30 days of study entry. Written informed consent was obtained from the parent or guardian of the subject.

Duration of treatment:
No treatment was administered during this long-term persistence stage of study 112036 (MENACWYTT-
048 EXT: 039 Y2, 3, 4, 5). There was one study visit at 36 months after vaccination.

Primary Outcome/Efficacy Variable:
Persistence of immunogenicity with respect to components of the investigational vaccine 36 months post
primary dose:
- rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥1:8.

Secondary Outcome/Efficacy Variable(s):
Immunogenicity with respect to components of the investigational vaccine 36 months post primary dose:
- rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥1:128 and titres.
- hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥1:4, ≥1:8 and titres.
- anti-PSA, anti-PSC, anti-PSW-135 and anti-PSY concentrations ≥0.3 μg/mL, ≥2.0 μg/mL and concentrations (using Enzyme-linked Immunosorbent assay or ELISA).

Note: The rSBA and anti-PS have been analysed at a different laboratory (Health Protection Agency or HPA) at Year 3, compared to previous years (GSK). To reflect this difference, which limits direct longitudinal comparison of the results of different timepoints, the rSBA and anti-PS tables have each been divided into two separate tables. One table presents Pre, Post and Month 24 timepoints tested at the GSK laboratory, while the other table presents only the Year 3 timepoint tested at the HPA laboratory. The data on hSBA testing, for which laboratory and method remained constant throughout the different timepoints of this persistence study, are presented in one table for all timepoints.

Synopsis Table 1: Study population (Total cohort at Month 36)		
Number of subjects	**ACWY-TT**	**MenCCRM**
Planned, N	502	168
Randomised, N (Total Cohort)	273	47
Completed, n (%)	273 (100)	47 (100)
Total Number Subjects Withdrawn, n (%)	0	0
Withdrawn due to Adverse Events, n (%)	0	0
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	0	0
Demographics	**ACWY-TT**	**MenCCRM**
N (Total Cohort)	273	47
Females:Males	129:144	22:25
Mean Age, months (SD)	49.0 (1.77)	49.3 (2.09)
White - Caucasian / European heritage, n (%)	271 (99.3)	47 (100)
ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039) MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)		

Results

Demography

Across the two vaccine groups, the mean age of the subjects in the According-to-protocol (ATP) cohort for persistence Year 3 was 49.1 months (range 46.0 to 57.0 months). 47.2% of the subjects were female, 52.8% of the subjects were male. The majority of the subjects in each group was of White/Caucasian/European heritage (99.4%).

Immunogenicity:

Immunogenicity analysis was performed on the ATP cohort for persistence at Year 3.
No confirmatory analyses were performed on primary or secondary objectives.

- At 36 months after primary vaccination in study MENACWY-TT-039, primary exploratory analysis showed HPA rSBA-MenA, HPA rSBA-MenC, HPA rSBA-MenW-135 and HPA rSBAMenY titres ≥1:8 were 61.4%, 35.9% , 49.8% and 35.0% in group ACWY-TT and 6.5%, 13.0%, 4.3% and 13.5% in group MenCCRM , respectively.
- At 36 months after primary vaccination, the percentages of subjects with hSBA-MenA, hSBAMenC, hSBA-MenW-135 and hSBA-MenY titres ≥1:4 were 37.8%, 80.6%, 82.3% and 73.6% in group ACWY-TT and 16.1%, 41.9%, 6.1% and 18.2% in group MenCCRM, respectively.
- At 36 months after primary vaccination, the percentages of subjects with HPA anti-PSA, HPA anti-PSC, HPA anti-PSW-135 and HPA anti-PSY concentrations ≥0.3μg/mL were 98.5%, 31.1%, 95.9% and 98.1% in group ACWY-TT and 76.9%, 20.0%, 44.0% and 86.4% in group MenCCRM, respectively.

Synopsis Table 2: Percentage of subjects with GSK rSBA titers equal to or above the cut-off values of 1:8 and 1:128 and GMTs (ATP cohort for persistence at Month 36)

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenA	ACWY-TT	PRE	122	39	32.0	23.8	41.0	27	22.1	15.1	30.5	13.1	9.5	18.2
		POST	258	258	100	98.6	100	258	100	98.6	100	1996.6	1798.9	2216.0
		M24	228	224	98.2	95.6	99.5	207	90.8	86.3	94.2	415.3	360.9	478.0
	MenCCRM	PRE	22	6	27.3	10.7	50.2	2	9.1	1.1	29.2	9.5	4.8	18.8
		POST	22	13	59.1	36.4	79.3	8	36.4	17.2	59.3	31.6	13.9	72.1
		M24	38	32	84.2	68.7	94.0	23	60.5	43.4	76.0	102.3	59.6	175.4
rSBA-MenC	ACWY-TT	PRE	122	35	28.7	20.9	37.6	15	12.3	7.0	19.5	10.5	7.9	13.9
		POST	256	256	100	98.6	100	240	93.8	90.0	96.4	463.1	416.2	515.2
		M24	235	210	89.4	84.7	93.0	115	48.9	42.4	55.5	104.2	84.7	128.2
	MenCCRM	PRE	19	6	31.6	12.6	56.6	1	5.3	0.1	26.0	9.3	4.9	17.9
		POST	46	44	95.7	85.2	99.5	24	52.2	36.9	67.1	153.2	102.8	228.2
		M24	39	28	71.8	55.1	85.0	19	48.7	32.4	65.2	58.5	31.7	107.9
rSBA-MenW-135	ACWY-TT	PRE	132	61	46.2	37.5	55.1	25	18.9	12.6	26.7	17.7	13.2	23.7
		POST	258	258	100	98.6	100	258	100	98.6	100	2231.1	2013.6	2472.0
		M24	236	232	98.3	95.7	99.5	211	89.4	84.8	93.0	372.4	323.4	428.9
	MenCCRM	PRE	27	12	44.4	25.5	64.7	7	25.9	11.1	46.3	20.6	9.2	46.0
		POST	25	14	56.0	34.9	75.6	6	24.0	9.4	45.1	27.2	12.2	60.7
		M24	39	22	56.4	39.6	72.2	16	41.0	25.6	57.9	39.7	19.5	80.5

(table continued on next page)

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenY	ACWY-TT	PRE	137	83	60.6	51.9	68.8	58	42.3	33.9	51.1	47.6	33.2	68.2
		POST	257	257	100	98.6	100	257	100	98.6	100	2551.3	2263.4	2875.7
		M24	237	231	97.5	94.6	99.1	195	82.3	76.8	86.9	405.4	337.4	487.1
	MenCCRM	PRE	27	20	74.1	53.7	88.9	14	51.9	31.9	71.3	79.4	35.9	175.9
		POST	26	19	73.1	52.2	88.4	13	50.0	29.9	70.1	77.2	33.6	177.3
		M24	40	33	82.5	67.2	92.7	26	65.0	48.3	79.4	169.1	89.6	319.1

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Day 0, pre-primary vaccination
POST = Day 42, 42 days post-primary vaccination with meningococcal vaccine
M24 = Month 24, 24 months post-primary vaccination
Note: At the 'POST' time point the MMRV sub-group of the MenCCRM group did not yet receive a meningococcal vaccination (the meningococcal vaccine was administered after the blood sampling at 42 days post-primary vaccination)

Synopsis Table 3: Percentage of subjects with HPA rSBA titers equal to or above the cut-off values of 1:8 and 1:128 and GMTs (ATP cohort for persistence at Month 36)

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenA	ACWY-TT	M36	241	148	61.4	54.9	67.6	58	24.1	18.8	30.0	20.4	16.4	25.2
	MenCCRM	M36	46	3	6.5	1.4	17.9	3	6.5	1.4	17.9	5.2	3.8	6.9
rSBA-MenC	ACWY-TT	M36	262	94	35.9	30.1	42.0	23	8.8	5.6	12.9	9.8	8.1	11.7
	MenCCRM	M36	46	6	13.0	4.9	26.3	3	6.5	1.4	17.9	5.7	4.2	7.7
rSBA-MenW-135	ACWY-TT	M36	261	130	49.8	43.6	56.0	87	33.3	27.6	39.4	24.9	19.2	32.4
	MenCCRM	M36	46	2	4.3	0.5	14.8	2	4.3	0.5	14.8	4.9	3.7	6.7
rSBA-MenY	ACWY-TT	M36	238	131	55.0	48.5	61.5	72	30.3	24.5	36.5	24.3	18.9	31.4
	MenCCRM	M36	37	5	13.5	4.5	28.8	1	2.7	0.1	14.2	5.5	4.1	7.4

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
M36 = Month 36, 36 months post-primary vaccination

Safety/reactogenicity: The safety analysis was performed on the Total vaccinated cohort. No unsolicited adverse events (AEs) were collected during year 3 persistence phase of the study.

Serious adverse events:

No serious adverse events (SAEs) considered to be possibly related to vaccination by the investigator, related to study participation, related to GSK concomitant medication or fatal SAEs were reported in the period between the last visit in the primary study and the Year 3 persistence visit.

Withdrawals due to adverse events /serious adverse events:

No subject withdrew because of an AE or SAE.

MAH Conclusion:

No confirmatory analyses were performed on primary or secondary objectives.
At 36 months after primary vaccination in study MENACWY-TT-039, primary exploratory analysis showed rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥1:8 were 61.4%, 35.9% , 49.8% and 35.0% in group ACWY-TT and 6.5%, 13.0%, 4.3% and 13.5% in group MenCCRM , respectively.
No unsolicited AEs were collected during year 3 persistence phase of the study. No SAEs considered to be possibly related to vaccination by the investigator or considered related to study participation were reported during the Year 3 persistence phase of the study.

Assessor's comments: This study report presents data on persistence of antibody 3 years post-vaccination.
The change from GSK to HPA determination of rSBA and anti-PS complicates interpretation of the results. However no change in methodology for hSBA testing occurred.

The clinical expert overview states that a full report describing antibody persistence and antibody from years 2 through 4 after vaccination and the immunogenicity and safety of a booster dose of Nimenrix will be written when the results of the year 4 persistence study and booster phase are available. Also the Company plan to update the SmPC with persistence data when results for ongoing studies are available and plan to submit a type II variation at the beginning of 2013. No SmPC changes are proposed to follow from this procedure (Art P46 010).

5. P46 011
MenACWY-TT-071 study (eCTD 14)

The applicant submits to the EMA the final report for MenACWY-TT-071 a paediatric study in accordance with Article 46 of Regulation (EC) No 1901/2006. A short critical expert overview has also been provided.
The applicant states that the MenACWY-TT-071 study is a stand alone study.
The applicant states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product.

MenACWY-TT-071

This was a phase II, observer-blinded, multi-center, controlled study to assess the safety and immunogenicity of one dose of GlaxoSmithKline (GSK) Biologicals' meningococcal serogroup ACWY tetanus toxoid conjugate vaccine (MenACWY-TT) versus one dose of sanofipasteur's meningococcal serogroup A, C, W-135 and Y vaccine (Menactra®) in healthy subjects aged 10 through 25 years.

This study was conducted by 33 investigators in two countries: the United States (US) and Canada.

Study period:

Study initiation date: 19 August 2010
Study completion date: 01 March 2011
Data lock point: 10 November 2011 (active phase)
21 December 2011 (ESFU phase)

Objectives:

Primary:

To demonstrate the non-inferiority of MenACWY-TT (Lot A) when compared to *Menactra* in terms of the percentage of subjects with serum bactericidal activity (using human complement) against *N. meningitidis* serogroup A (hSBA-MenA), hSBA-MenC, hSBA-MenW-135, and hSBA-MenY with respect to vaccine response* one month after vaccination.
*Vaccine response was defined as an hSBA titer of at least 1:8 in subjects initially seronegative (hSBA titer < 1:4) and as a 4-fold increase in titer in subjects initially seropositive (hSBA titer ≥ 1:4).

Criterion for non-inferiority: For each serogroup separately, the lower limit of the two-sided 95% confidence interval (CI) for the percentage of subjects with hSBA vaccine response one month after vaccination (ACWY-A group minus ACWY-DT group) was greater than or equal to the pre-defined clinical limit of -10%.

Secondary:

Immunogenicity:

At one month after primary vaccination with MenACWY-TT Lot A, Lot B or *Menactra*:

- To evaluate the clinical comparability of the two lots of MenACWY-TT conjugate vaccine with respect to the hSBA geometric mean titers (GMTs) for *Neisseria meningitidis* (*N. meningitidis)* serogroups A, C, W-135, and Y.
- To evaluate the immunogenicity of MenACWY-TT (both lots) and of *Menactra* in all three groups in terms of the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥ 1:4, ≥ 1:8 and GMTs.

• To evaluate the immunogenicity of Lot B in terms of the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY vaccine response.

Safety:

To evaluate the safety of the MenACWY-TT Lot A, Lot B, and *Menactra* vaccines with respect to:

• Local and general solicited symptoms during the 4-day period (Day 0 - Day 3) following vaccination.
• Unsolicited non-serious adverse events (AEs) during the 31-day period (Day 0 - Day 30) following vaccination.
• Serious adverse events (SAEs) and new onset chronic illness(es) [NOCIs] (e.g. autoimmune disorders, asthma, type 1 diabetes and allergies) from administration of study vaccines through 6 months (Day 0 - Day 180) after vaccination

Study design:

Phase II, observer-blinded, multi-center, controlled study with three parallel groups. Subjects were randomized 1:1:1 to receive vaccination with

- MenACWY-TT Lot A (ACWY-A group: 68% O-acetylation of MenA polysaccharide [PS]),
- MenACWY-TT Lot B (ACWY-B group: 92% O-acetylation of MenA PS) or
- *Menactra* (ACWY-DT group).

Blood samples were taken prior to and one month after vaccination.

Number of subjects:

Planned: 1005 healthy subjects 10-25 years of age (335 per treatment group).

Enrolled: 1016 subjects.

Completed: 993 subjects.

Safety: Total vaccinated cohort: 1011 subjects (337 subjects in the ACWY-A group, 336 subjects in the ACWY-B group and 338 subjects in the ACWY-DT group).

Immunogenicity: According-to-protocol (ATP) cohort for immunogenicity: 951 subjects (317 subjects in the ACWY-A group, 320 subjects in the ACWY-B group and 314 subjects in the ACWY-DT group).

Diagnosis and criteria for inclusion:

Healthy males or females aged 10 to 25 years of age at the time of the vaccination who the investigator believed that they and/or their parent(s)/legally acceptable representative [LAR(s)] could and would comply with the requirements of the protocol. Subjects needed to have previously completed routine childhood vaccinations to the best of the subject's/LAR's knowledge and could not have a previous history of having been administered a meningococcal congugate or PS vaccine. Females had to be of non-childbearing potential. If they were of childbearing potential, they had to practice and agree on adequate contraception for 30 days prior to vaccination until two months after vaccination, and have a negative pregnancy test on the day of vaccination. Written informed consent was obtained from the subjects or from the subjects' parents/LARs, as appropriate.

Study vaccine, dose, mode of administration, lot no.:

Vaccination schedule/site:

A single vaccine dose of MenACWY-TT was administered intramuscularly (IM) in the non-dominant (ND) deltoid in all subjects.

Vaccine composition/dose/lot number:

The MenACWY-TT vaccine consisted of 5 μg of meningococcal polysaccharide A (PSA), 5 μg of PSC,
5 μg of PSW-135 and 5 μg of PSY, conjugated to ~44 μg tetanus toxoid (TT). The vaccine was supplied
as a lyophilized pellet in a monodose vial for delivery of 0.5 mL volume after reconstitution with the
supplied saline diluent. The lot numbers for the vaccines were AMECA006C (Lot A) and DMECA010A (Lot B) for the pellet and AD02B290C for the diluent.

Reference vaccine/Comparator, dose and mode of administration, lot no.:

Vaccination schedule/site:

A single vaccine dose of *Menactra* was administered IM in the ND deltoid in all subjects.

Vaccine composition/dose/lot number:

The *Menactra* vaccine consisted of 4 μg of PSA, 4 μg of PSC, 4 μg of PSW-135 and 4 μg of PSY conjugated to ~48 μg diphtheria toxoid (DT). The vaccine was supplied as a clear to slightly turbid liquid in a monodose vial for delivery of 0.5 mL volume. The lot number for the vaccine was U3361AA.

Duration of treatment:

The intended duration of the study was approximately six months per subject, one month active phase and an additional five months of extended safety follow-up (ESFU).

Criteria for evaluation:

Immunogenicity:

Primary endpoint:

Immunogenicity in all subjects with respect to components of the investigational vaccine and the control vaccine:

- hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY vaccine response* in the ACWY-A group and the ACWY-DT group.

* Vaccine response was defined as an hSBA titer of at least 1:8 in subjects initially seronegative (hSBA titer < 1:4) and as a 4-fold increase in titer in subjects initially seropositive (hSBA titer ≥ 1:4).

Secondary endpoints:

Immunogenicity in all subjects with respect to components of the investigational vaccines and the control vaccine (on secondary read-outs):

- hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥ 1:4, ≥ 1:8, and GMTs prior to and one month after vaccination in all groups.
- Vaccine response in the ACWY-B group.

Safety:

Secondary endpoints:

Solicited local and general symptoms:

- Occurrence of each solicited local (any and grade 3) and general symptom (any, grade 3, related) within 4 days (Day 0 - Day 3) following vaccination.

Unsolicited symptoms:

• Occurrence of unsolicited non-serious AEs within 31 days (Day 0 - Day 30) after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
• Occurrence of SAEs and NOCIs (e.g. autoimmune disorders, asthma, type I diabetes, and allergies) from the time of vaccination (Month 0) through 6 months after study vaccination.

Summary of Results:

Demography:

The demographic profile of the subjects of the three vaccine groups was comparable with respect to mean age, gender and racial distribution. The mean age of the subjects at the time of enrolment across the three vaccine groups was 16.3 years (range from 10 to 25 years). A similar number of males and females was enrolled overall (female/male ratio of 1.05). Around 74% of subjects from all three vaccine groups were from White-Caucasian/European heritage. Most remaining subjects were of African/African American heritage (10.5%), Asian-Central/South Asian heritage (5.3%) and of other origin (mixed races, 5.9%).

Immunogenicity:

The primary analysis of immunogenicity was performed on the ATP cohort for immunogenicity. Since the percentage of enrolled subjects with serological results available excluded from this ATP cohort was less than 5%, no supplementary analysis based on the Total vaccinated cohort was performed.

Primary objective (Synopsis table 1):

The non-inferiority of MenACWY-TT (Lot A) when compared to *Menactra* in terms of the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY vaccine response one month after vaccination was demonstrated since for each serogroup separately, the lower limit of the two-sided 95% CI for the difference between groups (ACWY-A minus ACWY-DT) was greater than the pre-defined clinical limit of -10%.

Synopsis table 1: Difference between ACWY-A and ACWY-DT groups in percentage of subjects with vaccine response to hSBA antibodies one month after the vaccination (ATP cohort for immunogenicity)

								Difference in vaccine response rate (ACWY-A minus ACWY-DT)		
		ACWY-A			ACWY-DT				95% CI	
Antibody	**Pre-vaccination status**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
hSBA-MenA	S-	231	175	75.8	211	144	68.2	7.51	-	-
	S+	79	43	54.4	86	47	54.7	-0.22	-	-
	Total	310	218	70.3	297	191	64.3	6.01	**-1.45**	13.44
hSBA-MenC	S-	108	98	90.7	90	86	95.6	-4.81	-	-
	S+	173	119	68.8	184	123	66.8	1.94	-	-
	Total	281	217	77.2	274	209	76.3	0.95	**-6.10**	8.00
hSBA-MenW-135	S-	184	158	85.9	192	145	75.5	10.35	-	-
	S+	95	40	42.1	97	40	41.2	0.87	-	-
	Total	279	198	71.0	289	185	64.0	6.95	**-0.76**	14.59
hSBA-MenY	S-	79	73	92.4	68	52	76.5	15.93	-	-
	S+	214	77	36.0	227	63	27.8	8.23	-	-
	Total	293	150	51.2	295	115	39.0	12.21	**4.17**	20.10

ACWY-A = MenACWY-TT Lot A; ACWY-DT = *Menactra;* S- = seronegative subjects (antibody titer < 1:4) prior to vaccination; S+ = seropositive subjects (antibody titer ≥ 1:4) prior to vaccination; Total = subjects either seropositive or seronegative prior to vaccination;
Vaccine response defined as:
For initially seronegative subjects: post-vaccination antibody titer ≥ 1:8 at one month post-vaccination
For initially seropositive subjects: antibody titer at one month post-vaccination ≥ 4-fold the pre-vaccination antibody titer
N = number of subjects with pre- and post-vaccination results available; n/% = number/percentage of subjects with a vaccine response, 95% CI = Standardized asymptotic 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Bold: LL of 95% CI is above non-inferiority limit of -10%.

Secondary objectives:

Meningococcal serogroup A, C, W-135 and Y bactericidal vaccine response (Synopsis table 2):

- The observed meningococcal bactericidal vaccine response rates for each of the four serogroups in the ACWY-A and ACWY-B groups following the administration of the MenACWY-TT vaccine ranged from 51.0% (hSBA-MenY in ACWY-B group) to 82.5% (hSBA-MenC in ACWY-B group). In the ACWY-DT group, the vaccine response rate ranged from 39.0% for hSBA-MenY to 76.3% for hSBA-MenC.

Synopsis table 2: Vaccine response for hSBA antibodies one month after the vaccination (ATP cohort for immunogenicity)

				Vaccine response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
hSBA-MenA	ACWY-A	S-	231	175	75.8	69.7	81.1
		S+	79	43	54.4	42.8	65.7
		Total	310	218	70.3	64.9	75.4
	ACWY-B	S-	221	166	75.1	68.9	80.7
		S+	79	48	60.8	49.1	71.6
		Total	300	214	71.3	65.9	76.4
	ACWY-DT	S-	211	144	68.2	61.5	74.5
		S+	86	47	54.7	43.5	65.4
		Total	297	191	64.3	58.6	69.8
hSBA-MenC	ACWY-A	S-	108	98	90.7	83.6	95.5
		S+	173	119	68.8	61.3	75.6
		Total	281	217	77.2	71.9	82.0
	ACWY-B	S-	92	85	92.4	84.9	96.9
		S+	182	141	77.5	70.7	83.3
		Total	274	226	82.5	77.5	86.8
	ACWY-DT	S-	90	86	95.6	89.0	98.8
		S+	184	123	66.8	59.5	73.6
		Total	274	209	76.3	70.8	81.2
hSBA-MenW-135	ACWY-A	S-	184	158	85.9	80.0	90.6
		S+	95	40	42.1	32.0	52.7
		Total	279	198	71.0	65.3	76.2
	ACWY-B	S-	179	154	86.0	80.1	90.8
		S+	91	42	46.2	35.6	56.9
		Total	270	196	72.6	66.9	77.8
	ACWY-DT	S-	192	145	75.5	68.8	81.4
		S+	97	40	41.2	31.3	51.7
		Total	289	185	64.0	58.2	69.6
hSBA-MenY	ACWY-A	S-	79	73	92.4	84.2	97.2
		S+	214	77	36.0	29.6	42.8
		Total	293	150	51.2	45.3	57.1
	ACWY-B	S-	79	75	94.9	87.5	98.6
		S+	215	75	34.9	28.5	41.7
		Total	294	150	51.0	45.2	56.9
	ACWY-DT	S-	68	52	76.5	64.6	85.9
		S+	227	63	27.8	22.0	34.1
		Total	295	115	39.0	33.4	44.8

ACWY-A = MenACWY-TT Lot A; ACWY-B = MenACWY-TT Lot B; ACWY-DT = Menactra; S- = seronegative subjects (antibody titer < 1:4 for hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY) prior to vaccination;

S+ = seropositive subjects (antibody titer ≥ 1:4 for hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY) prior to vaccination; Total = subjects either seropositive or seronegative prioir to vaccination;
Vaccine response defined as:
For initially seronegative subjects: antibody titer ≥ 1:8 at one month post-vaccination
For initially seropositive subjects: antibody titer at one month post-vaccination ≥ 4-fold the pre-vaccination antibody titer
N = number of subjects with both pre- and post-vaccination results available; n/% = number/percentage of responders; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Meningococcal serogroup A, C, W-135 and Y bactericidal antibody titers (Synopsis table 3):
- The pre-vaccination percentage of subjects with titers ≥ 1:4 ranged between 25.5% (hSBA-MenA in ACWY-A) and 77.0% (hSBA-MenY in ACWY-DT) in the three study groups.
- One month post-vaccination, the percentage of subjects with titers ≥ 1:4 for the four serogroups ranged between 73.1% (hSBA-MenA in ACWY-DT) and 98.4% (hSBA-MenY in ACWY-B). The percentage of subjects with hSBA titers ≥ 1:8 varied from 72.5% (hSBA-MenA in ACWY-DT) to 98.4% (hSBA-MenY in ACWY-B).

Synopsis table 3: Percentage of subjects with hSBA titers equal to or above the cut-off values of 1:4 and 1:8 and GMTs (ATP cohort for immunogenicity)

				≥ 1:4				≥ 1:8				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
hSBA-MenA	ACWY-A	PRE	310	79	25.5	20.7	30.7	61	19.7	15.4	24.5	3.6	3.1	4.0
		PI(M1)	315	253	80.3	75.5	84.6	251	79.7	74.8	84.0	54.2	43.5	67.4
	ACWY-B	PRE	309	84	27.2	22.3	32.5	65	21.0	16.6	26.0	3.6	3.2	4.1
		PI(M1)	309	243	78.6	73.6	83.1	242	78.3	73.3	82.8	49.6	39.6	62.1
	ACWY-DT	PRE	306	89	29.1	24.1	34.5	67	21.9	17.4	27.0	3.6	3.2	4.1
		PI(M1)	305	223	73.1	67.8	78.0	221	72.5	67.1	77.4	41.3	32.3	52.9
hSBA-MenC	ACWY-A	PRE	288	175	60.8	54.9	66.4	174	60.4	54.5	66.1	15.6	12.3	19.9
		PI(M1)	307	295	96.1	93.3	98.0	295	96.1	93.3	98.0	687.1	510.5	924.9
	ACWY-B	PRE	286	188	65.7	59.9	71.2	185	64.7	58.8	70.2	16.0	12.8	20.0
		PI(M1)	304	293	96.4	93.6	98.2	292	96.1	93.2	97.9	755.8	557.3	1025.0
	ACWY-DT	PRE	289	197	68.2	62.5	73.5	193	66.8	61.0	72.2	18.0	14.4	22.6
		PI(M1)	296	291	98.3	96.1	99.4	291	98.3	96.1	99.4	543.3	411.2	718.0
hSBA-MenW-135	ACWY-A	PRE	293	99	33.8	28.4	39.5	99	33.8	28.4	39.5	7.7	6.1	9.7
		PI(M1)	298	272	91.3	87.5	94.2	272	91.3	87.5	94.2	174.5	138.6	219.6
	ACWY-B	PRE	290	98	33.8	28.4	39.6	97	33.4	28.0	39.2	7.6	6.0	9.6
		PI(M1)	292	262	89.7	85.7	93.0	262	89.7	85.7	93.0	161.6	128.3	203.5
	ACWY-DT	PRE	299	102	34.1	28.8	39.8	101	33.8	28.4	39.4	7.4	5.9	9.2
		PI(M1)	297	247	83.2	78.4	87.2	247	83.2	78.4	87.2	101.7	77.9	132.7
hSBA-MenY	ACWY-A	PRE	296	215	72.6	67.2	77.6	215	72.6	67.2	77.6	45.7	35.9	58.2
		PI(M1)	313	307	98.1	95.9	99.3	307	98.1	95.9	99.3	349.1	298.1	408.8
	ACWY-B	PRE	306	224	73.2	67.9	78.1	223	72.9	67.5	77.8	49.8	39.1	63.4
		PI(M1)	307	302	98.4	96.2	99.5	302	98.4	96.2	99.5	387.4	329.7	455.1
	ACWY-DT	PRE	304	234	77.0	71.8	81.6	234	77.0	71.8	81.6	55.3	43.7	69.9
		PI(M1)	305	287	94.1	90.8	96.5	287	94.1	90.8	96.5	253.8	204.9	314.5

ACWY-A = MenACWY-TT Lot A; ACWY-B = MenACWY-TT Lot B; ACWY-DT = Menactra; GMT = geometric mean antibody titer calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with titer within the specified range; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = Pre-vaccination at Month 0; PI(M1) = Post-vaccination at Month 1

Safety:

The primary analysis of safety was performed on the Total vaccinated cohort. Since less than 5% of the
enrolled subjects were eliminated from the ATP cohort for analysis of safety, no supplementary analysis
was performed on the ATP cohort for safety.

Overall incidence of AEs:

- At least one symptom (solicited or unsolicited) was reported in 70.0%, 66.1% and 70.1% of subjects in the ACWY-A, ACWY-B and ACWY-DT groups, respectively. The incidence of subjects with local symptoms was 58.8%, 56.3% and 59.5%, respectively and the incidence of subjects with general symptoms was 44.8%, 39.3% and 42.3%, respectively.

Solicited local AEs:

- The predominant solicited local symptom during the 4-day post-vaccination period was pain at the injection site, reported by 51.4%, 50.8%, 55.4% of subjects in the ACWY-A, ACWY-B and ACWY-DT groups, respectively. A much smaller percentage of these subjects reported pain with grade 3 intensity, ranging between 0.6% and 2.4% across all vaccine groups.

Solicited general AEs:

- Across the three vaccine groups, the most common solicited general symptom was fatigue with an incidence of 27.3% to 29.2%. Headache was reported by 25.5% to 26.4% and gastrointestinal symptoms by 13.1% to 13.5% of subjects across the three vaccine groups. The incidence of fever (defined as temperature ≥37.5° C [99.5° F] measured by any method) ranged from 4.3% to 5.2% across the three vaccine groups. Only one subject in the ACWY-A group reported fever above 39.5° C.
- A small percentage (2.7% at most) of subjects had solicited general symptoms with grade 3 intensity after vaccination in the three vaccine groups. The majority of the reported solicited general symptoms were attributed a causal relationship to the vaccination by the investigators.

Unsolicited AEs:

- At least one unsolicited symptom during the 31-day post-vaccination period was reported for 105 (31.2%), 76 (22.6%) and 85 (25.1%) subjects in the ACWY-A, ACWY-B and ACWY-DT groups, respectively.
- At least one unsolicited symptom with grade 3 intensity was reported in 17 (5.0%), 13 (3.9%) and 16 (4.7%) subjects in the ACWY-A, ACWY-B and ACWY-DT groups, respectively. The most common grade 3 symptom was cough (0.9% in the ACWY-A and ACWY-DT groups, and 0% in the ACWY-B group). All other separate symptoms occurred in at most 2 subjects per treatment group (Table 25).

- Unsolicited symptoms related to vaccination were reported in 25 (7.4%), 15 (4.5%) and 27 (8.0%) subjects in the ACWY-A, ACWY-B and ACWY-DT groups, respectively. The most frequently reported unsolicited symptoms with causal relationship to vaccination were injection site reaction in the ACWY-A group (1.2%) and injection site hematoma in the ACWY-B group (0.9%) and in the ACWY-DT group (1.5%)

- Grade 3 unsolicited symptoms causally related to vaccination were reported by five subjects in the ACWY-A group and two subjects each in the ACWY-B and ACWY-DT groups. Only pain and chills were reported by two subjects in the ACWY-A and ACWY-B groups, respectively, while all other separate symptoms were reported by one subject per treatment group

New Onset of Chronic Illness:

• At least one NOCI was reported from Dose 1 up to the study end by three (0.9%) subjects in the ACWY-A group and included hypersensitiviy, insulin resistance, asthma and bronchial hyperreactivity

Percentage of subjects reporting New Onset of Chronic Illness classified by MedDRA Primary System Organ Class and Preferred Term from Dose 1 up to study end (Total vaccinated cohort)

		ACWY-A N = 337				ACWY-B N = 336				ACWY-DT N = 338			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		3	0.9	0.2	2.6	0	0.0	0.0	1.1	0	0.0	0.0	1.1
Immune system disorders (10021428)	Hypersensitivity (10020751)	1	0.3	0.0	1.6	0	0.0	0.0	1.1	0	0.0	0.0	1.1
Metabolism and nutrition disorders (10027433)	Insulin resistance (10022489)	1	0.3	0.0	1.6	0	0.0	0.0	1.1	0	0.0	0.0	1.1
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	1	0.3	0.0	1.6	0	0.0	0.0	1.1	0	0.0	0.0	1.1
	Bronchial hyperreactivity (10066091)	1	0.3	0.0	1.6	0	0.0	0.0	1.1	0	0.0	0.0	1.1

ACWY-A = MenACWY-TT lot A
ACWY-B = MenACWY-TT lot B
ACWY-DT = *Menactra*
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Serious adverse events:
• From Dose 1 up to the study end, SAEs were reported by one subject in the ACWY-A group (asthma), five subjects in the ACWY-B group (tooth infection, appendicitits, asthma, influenza, pneumonia and hypoxia) and two subjects in the ACWY-DT group (jaw fracture and postprocedural haematoma). None of these SAEs were considered by the investigator to be causally related to study vaccination. No fatal SAEs were reported during the study.

Listing of SAEs from Dose 1 up to study end (Total vaccinated cohort)

Group	Sub. No.	Case Id	Age at onset (Year)	Sex	Verbatim	Preferred term	System Organ Class	MED type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
ACWY-A	214	R0013554A	10	M	Exacerbation of asthma	Asthma	Respiratory, thoracic and mediastinal disorders	HO	1	13	6	3	N	Recovered/resolved
ACWY-B	104	R0016458A	15	F	Tooth infection	Tooth infection	Infections and infestations	HO	1	96	5	3	N	Recovered/resolved
	306	R0016612A	20	F	Appendicitis	Appendicitis	Infections and infestations	HO	1	80	4	3	N	Recovered/resolved
	619	R0016915A	16	M	Exacerbation of pre-existing asthma	Asthma	Respiratory, thoracic and mediastinal disorders	HO	1	138	9	2	N	Recovered/resolved
			16		Influena a	Influenza	Infections and infestations	HO	1	138	9	2	N	Recovered/resolved
			16		Pneumonia	Pneumonia	Infections and infestations	HO	1	138	9	2	N	Recovered/resolved
	735	R0014427A	10	M	Hypoxia	Hypoxia	Respiratory, thoracic and mediastinal disorders	HO	1	39	51	3	N	Recovered/resolved
			10		Pneumonia	Pneumonia	Infections and infestations	HO	1	39	51	3	N	Recovered/resolved
	954	R0014969A	11	M	Acute appendicitis	Appendicitis	Infections and infestations	HO	1	94	3	3	N	Recovered/resolved
ACWY-DT	856	R0013174A	20	F	Fractured jaw	Jaw fracture	Injury, poisoning and procedural complications	HO	1	0	70	2	N	Recovered/resolved
	1863	R0014506A	23	F	Post operative hematoma	Post procedural haematoma	Injury, poisoning and procedural complications	HO	1	11	8	3	N	Recovered/resolved

ACWY-A = MenACWY-TT lot A
ACWY-B = MenACWY-TT lot B
ACWY-DT = Menactra

Pregnancies:
During the 31-day follow-up period post-vaccination, two subjects became pregnant. An additional 8 subjects became pregnant after the 31-day post-vaccination period.

MAH Conclusions:

- The non-inferiority of MenACWY-TT (Lot A) when compared to *Menactra* in terms of the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY vaccine response one month after vaccination was demonstrated (all the lower limits of the two sided 95% CI for the difference between groups were greater than or equal to -10%).
- At least one unsolicited symptom during the 31-day post-vaccination period was reported for 105 (31.2%), 76 (22.6%) and 85 (25.1%) subjects in the ACWY-A, ACWY-B and ACWY-DT groups, respectively. Grade 3 unsolicited events were infrequent (at least one event reported in 5.0% of subjects at most). At least one NOCI was reported from Dose 1 up to the study end for three (0.9%) subjects in the ACWY-A group (hypersensitiviy, insulin resistance, asthma and bronchial hyperreactivity). From Dose 1 up to the study end, SAEs were reported by one subject in the ACWY-A group (asthma), five subjects in the ACWY-B group (tooth infection, appendicitits, asthma, influenza, pneumonia and hypoxia) and two subjects in the ACWY-DT group (jaw fracture and post-procedural haematoma). None of the SAEs were considered by the investigator to be causally related to study vaccination. No fatal SAEs were reported during the study. In this study, the study vaccine was generally well tolerated.

Assessor's comment: The MAH conclusions are agreed. No SmPC changes result from this study.

6. P46 012
MenACWY-TT-057 PRI & BST (eCTD sequence 15)

The applicant hereby submits to the EMA the final report for the paediatric study MenACWY-TT-057 in accordance with Article 46 of Regulation (EC) No 1901/2006. A short critical expert overview has also been provided. The applicant states that the MenACWY-TT-057 study is a stand alone study.

The applicant states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product.

MENACWY-TT-057 PRI & BST

Study detailed title

A Phase III, open, randomized, controlled, multicenter study to assess the safety and immunogenicity of GlaxoSmithKline's Biologicals' (GSK Biologicals) *Neisseria meningitidis* serogroups A, C, W-135, Y-tetanus toxoid conjugate (MenACWY-TT) vaccine as compared to GSK Biologicals' *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine combined (Hib-MenCY-TT) in healthy toddlers 12-15 months of age who were primed at 2, 4 and 6 months of age with Hib-MenCY-TT and Pediarix®, and to assess the safety and immunogenicity of MenACWY-TT co-administered with Infanrix® in healthy toddlers 15-18 months of age who were primed with Hib-MenCY-TT and Pediarix® at 2, 4, and 6 months of age as compared to the administration of Infanrix® alone in healthy toddlers 15-18 months of age who were primed with ActHIB® and Pediarix® at 2, 4 and 6 months of age.

Hib-MenCY-TT (Menhibrix) was approved in the US in June 2012 for use in children 6 weeks of age through 18 months of age for active immunisation to prevent invasive disease caused by *Neisseria meningitidis* serogroups C and Y and *Haemophilus influenzae* type b.

Study center(s):

The study was conducted at 60 centers located in the United States (US).

Study period:

Study initiation date: 09 December 2008. Study completion date: 19 August 2010. Data lock point: 28 October 2011

Objectives:

The table below presents the definition of group names used in the criteria for evaluation Study group names and treatments.

Study group names and treatments

Group name	Group treatment			
	Primary Vaccination	Fourth Dose Vaccination		Blood Draw
	3 doses at 2, 4, 6 months of age (Visits1,2 and 3)	at 12-15 months of age(Visit4)	at 15-18 months of age (Visit6)	
ACWY-TT	Hib-MenCY-TT + *Pediarix*	MenACWY-TT	*Infanrix*	Visit 5: 13-16 months of age Visit 7: 16-19 months of age
Hib-CY	Hib-MenCY-TT + *Pediarix*	Hib-MenCY-TT	*Infanrix*	Visit 5: 13-16 months of age Visit 7: 16-19 months of age
Co-ad	Hib-MenCY-TT + *Pediarix*	Randomization only No vaccination	MenACWY-TT + *Infanrix*	Visit 6: 15-18 months of age Visit 7: 16-19 months of age
Control	*Pediarix* + *ActHIB*	Randomization only No vaccination	*Infanrix*	Visit 7: 16-19 months of age

Note: The group names refer to the treatment groups after randomization in the Fourth Dose Phase. The visit at 15-18 months of age was called Visit 6 for all groups, despite the fact that the subjects in the Co-ad and Control groups did not come in for the blood draw at Visit 5.

Primary objectives were assessed in a hierarchical manner. A co-primary objective was only met if the statistical criterion for that objective was met as well as the statistical criteria for all previous co-primary objectives.

1. To demonstrate the immunogenicity of a fourth dose of MenACWY-TT when administered at 12–15 months of age (ACWY-TT group), with respect to antibody responses as measured by hSBA for serogroups A, C, Y and W-135.
Criteria for evaluation:
- For serogroup C and Y separately (*N. meningitidis* serogroup C [MenC] and *N. meningitidis* serogroup Y [MenY]), the lower limits of the 2-sided 95% confidence intervals (CIs) for the percentage of subjects with hSBA titers ≥1:8 (ACWY-TT group Visit 5 blood sample minus the Hib-CY group Visit 5 blood sample) were greater than or equal to the pre-defined clinical limit of -10%.
- For serogroup A and W-135 separately (*N. meningitidis* serogroup A [MenA] and *N. meningitidis* serogroup W-135 [MenW-135]), one month after the MenACWY-TT dose (Visit 5 blood sample), the lower limits of the 2-sided 95% CIs for the percentage of subjects with hSBA antibody titers ≥1:8 were greater than or equal to the pre-defined clinical limit of 80%.

2. To demonstrate the immunogenicity of a fourth dose of MenACWY-TT co-administered with *Infanrix* at 15-18 months of age (Co-ad group), with respect to antibody responses as measured by hSBA for serogroups A, C, Y and W-135.
Criteria for evaluation:
- For serogroup C and Y separately, the lower limits of the 2-sided 95% CI for the percentage of subjects with hSBA titers ≥1:8 (Co-ad group Visit 7 blood sample minus the Hib-CY group Visit 5 blood sample) were greater than or equal to the pre-defined clinical limit of -10%.
- For serogroup A and W-135 separately (MenA and MenW-135), one month after the MenACWY-TT dose (Co-ad group, Visit 7 blood sample), the lower limits of the 2-sided 95% CIs for the percentage of subjects with hSBA antibody titers ≥1:8 were greater than or equal to the pre-defined clinical limit of 80%.

3. To demonstrate the non-inferiority of the antibody responses to diphtheria toxoid (anti-D) and antibody responses to tetanus toxoid (anti-T) when *Infanrix* was co-administered with MenACWY-TT at 15-18 months of age (Co-ad group) as compared to *Infanrix* administered alone at 15-18 months o**f** age (Control group) with respect to antibody concentrations ≥1.0 IU/mL.
Criteria for evaluation:
- For each antibody separately (anti-D and anti-T), one month after vaccination with *Infanrix* (Visit 7 blood sample), the lower limits of the standardized asymptotic 95% CIs on the group differences (Co-ad group Visit 7 blood sample minus the Control group Visit 7 blood sample) of the percentage of subjects with anti-D and anti-T antibody concentrations ≥1.0 IU/mL were greater than or equal to the pre-defined clinical limit of -10%.

4. To demonstrate the non-inferiority of the antibody responses to pertussis toxoid (anti-PT), filamentous hemagglutinin (anti-FHA), and pertactin (anti-PRN) when *Infanrix* was co-administered with MenACWY-TT at 15-18 months of age (Co-ad group) as compared to *Infanrix* administered alone (Control group) with respect to geometric mean antibody concentrations (GMCs) for the three pertussis antigens.
Criteria for evaluation:
- For each antigen separately (anti-PT, anti-FHA, and anti-PRN), one month after vaccination with *Infanrix* (Visit 7 blood sample), the lower limits of the 2-sided 95% CIs on the group ratios (Co-ad group Visit 7 blood sample over the Control Visit 7 blood sample) in GMCs as measured by ELISA were greater than or equal to the pre-defined clinical limit of 0.67.

5. To demonstrate the non-inferiority of a fourth dose of MenACWY-TT (ACWY-TT group) as compared to Hib-MenCY-TT (Hib-CY group) when administered at 12–15 months of age, with respect to antibody responses as measured by hSBA for serogroups C and Y.
Criteria for evaluation:
- For serogroup C and Y separately, the lower limits of the 2-sided 95% CIs on the group ratios (ACWY-TT group Visit 5 blood sample over the Hib-CY group Visit 5 blood sample) in geometric mean antibody titers (GMTs) as measured by hSBA were greater than or equal to the pre-defined clinical limit of 0.5.

6. To demonstrate the non-inferiority of a fourth dose of MenACWY-TT co-administered with *Infanrix* at 15-18 months of age (Co-ad group) as compared to Hib-MenCY-TT when administered at 12–15 months of age (Hib-CY group, with respect to antibody responses as measured by hSBA for serogroups C and Y.
Criteria for evaluation:

• For serogroup C and Y separately, the lower limits of the 2-sided 95% CIs on the group ratios (Co-ad group Visit 7 blood sample over the Hib-CY group Visit 5 blood sample) in GMTs as measured by hSBA objectives were greater than or equal to the pre-defined clinical limit of 0.5.

Secondary:

Immunogenicity

• To evaluate the immunogenicity of *Infanrix* administered at 15-18 months of age given after either MenACWY-TT or Hib-MenCY-TT dose given at 12-15 months (i.e., ACWY-TT group and Hib-CY group, respectively) as compared to *Infanrix* administered alone at 15-18 months of age after 3-dose priming with *Pediarix* and *ActHIB* (i.e. Control) with respect to antibody responses to diphtheria, tetanus and pertussis one month after vaccination

• To evaluate the immunogenicity of a dose of MenACWY-TT administered at 12-15 months of age (ACWY-TT group) as compared to MenACWY-TT co-administered with *Infanrix* at 15-18 months of age (Co-ad group) with respect to the four *Neisseria meningitidis* serogroups, one month after vaccination.

Safety

• To evaluate the safety of Hib-MenCY-TT co-administered with *Pediarix* as 3 primary doses with respect to:

− serious adverse events, new onset chronic illnesses, and adverse events resulting in emergency room (ER) visits from day 0 after the primary vaccination at Visit 1 through Day 30 post-dose 3 and up to/excluding the first visit in the Fourth Dose Phase (Visit 4 or six months after the final primary vaccination for subjects who discontinued from the study).

• To evaluate the safety of a fourth dose of MenACWY-TT administered at 12-15 months of age followed by *Infanrix* and of MenACWY-TT co-administered with *Infanrix* at 15-18 months of age as compared to a fourth dose of Hib-MenCY-TT administered at 12-15 months of age followed by *Infanrix* and as compared to a dose of *Infanrix* at 15-18 months of age with respect to:

− solicited local reactions (pain, redness and swelling) on Days 0-7 following vaccination,

− solicited systemic reactions (drowsiness, irritability, loss of appetite, and fever [defined as temperature by any measurement method ≥100.4°F/38.0°C]) on Days 0-7 following vaccination,

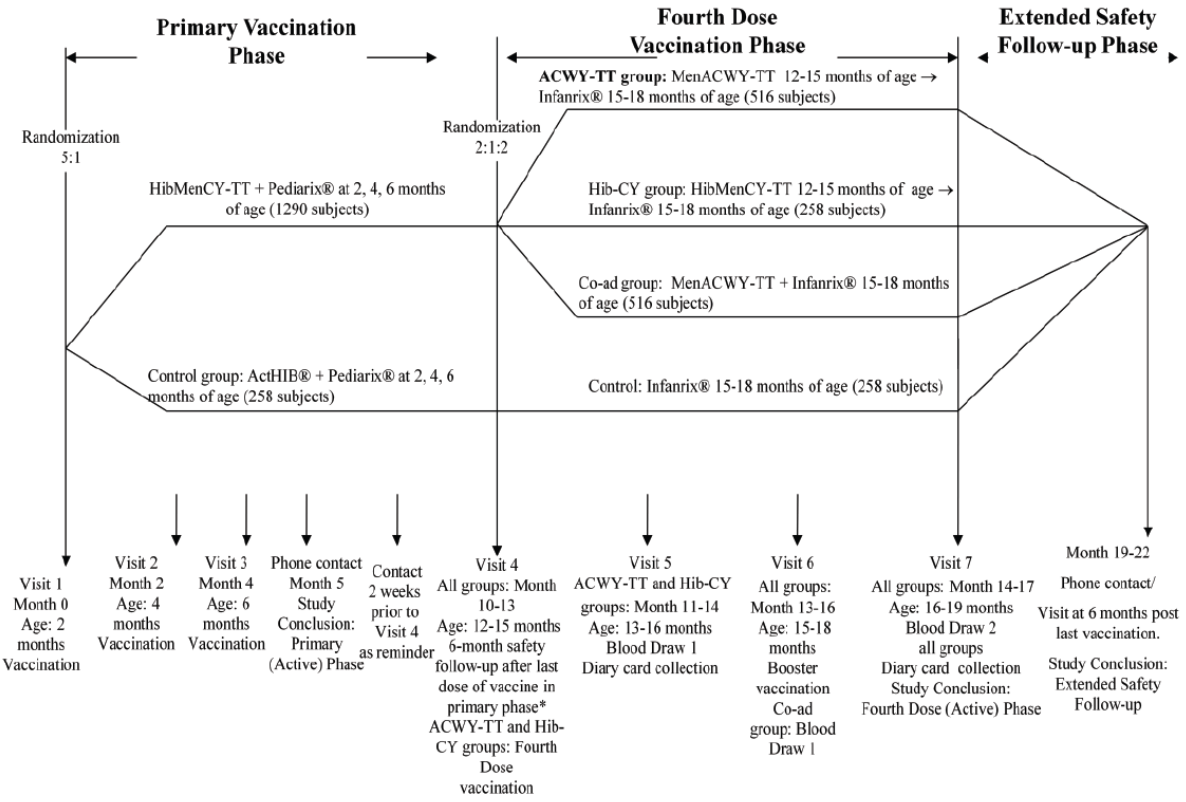
− unsolicited adverse events on Days 0-30 after vaccination,

− serious adverse events, new onset chronic illnesses, rash and adverse events resulting in ER visits from Visit 4 through six months after the last Fourth Dose Phase vaccination.

Note: Serious adverse events, new onset chronic illnesses, rash and adverse events resulting in ER visits were reported during the entire Fourth Dose Phase and the Extended Safety Follow-up Phase after the fourth dose vaccination (i.e. from Visit 4 to 6 months after the last vaccination) for subjects in all treatment groups even though the subjects in the Co-ad and Control groups were not vaccinated until Visit 6.

Study design:

Note: The Control and Co-ad groups were not required to come in for Visits 4 and 5, so the first visit they came in for in the Fourth Dose Phase was Visit 6 (at which they received their first Fourth Dose Phase vaccination). Even though this was their fourth visit, it was called Visit 6 and not Visit 4.



* Study personnel will contact the parents/guardians of subjects who are withdrawn from the study before Visit 4 by phone to complete the 6-month safety follow-up.

Number of subjects:
Planned- Primary Phase: 1548 healthy subjects (1290 in the HibCYpr group and 258 in the Control)
Enrolled-Primary Phase: 1558 healthy subjects (1276 in the HibCYpr group and 282 in the Control)
Vaccinated-Primary Phase: 1554 healthy subjects (1272 in the HibCYpr group and 282 in the Control)
Completed-Primary Phase: 1447 healthy subjects (1182 in the HibCYpr group and 265 in the Control)

Enrolled-Fourth Dose Phase: 1346 healthy subjects (438 in the ACWY-TT group, 234 in the Hib-CY group, 426 in the Co-ad group, and 248 in the Control)
Vaccinated- Fourth Dose Phase: 1303 healthy subjects (432 in the ACWY-TT group, 229 in the Hib-CY group, 409 in the Co-ad group, and 233 in the Control)
Completed-Fourth Dose Phase: 1238 healthy subjects (405 in the ACWY-TT group, 210 in the Hib-CY group, 396 in the Co-ad group, and 227 in the Control)
Safety-Fourth Dose Phase: According-to-protocol (ATP) cohort: 1143 healthy subjects (369 in the ACWYTT group, 197 in the Hib-CY group, 367 in the Co-ad group, and 210 in the Control)
Immunogenicity-Fourth Dose Phase: ATP cohort: 955 healthy subjects (309 in the ACWY-TT group, 168 in the Hib-CY group, 303 in the Co-ad group, and 175 in the Control)

Diagnosis and criteria for inclusion:
Healthy males or females born after 36 weeks of gestation who were between, and including, 6 and 12 weeks of age (+ 6 days) at the time of the first vaccination. Subjects for whom the investigator believed that parents/guardians could and would comply with the requirements of the protocol (e.g., completion of the diary card, return for follow-up visits). Parent or guardian of the subject provided written informed consent. For inclusion in the Fourth Dose Phase, subjects had to receive all three doses in the Primary Phase.

Study vaccine, dose, mode of administration, lot no.:
Vaccination schedule /site:

Synopsis Table 1: Vaccine Administration

Group	Visits	Vaccine	Route	Site	Side
ACWY-TT	1, 2, 3	Hib-MenCY-TT	IM	Thigh	Left
	1, 2, 3	*Pediarix*	IM	Thigh	Right
	4	MenACWY-TT	IM	Arm or thigh	Left
	6	*Infanrix*	IM	Arm or thigh	Left
Hib-CY	1, 2, 3	Hib-MenCY-TT	IM	Thigh	Left
	1, 2, 3	*Pediarix*	IM	Thigh	Right
	4	Hib-MenCY-TT	IM	Arm or thigh	Left
	6	*Infanrix*	IM	Arm or thigh	Left
Co-ad	1, 2, 3	Hib-MenCY-TT	IM	Thigh	Left
	1, 2, 3	*Pediarix*	IM	Thigh	Right
	6	MenACWY-TT	IM	Arm or thigh	Left
	6	*Infanrix*	IM	Arm or thigh	Right
Control	1, 2, 3,	*ActHIB*	IM	Thigh	Left
	1, 2, 3	*Pediarix*	IM	Thigh	Right
	6	*Infanrix*	IM	Arm or thigh	Left

IM = intramuscular

Vaccine composition /dose /lot number:

Table 2s: Study and reference (control) vaccines (including concomitantly administered vaccines): formulations, presentations and lot numbers

Vaccine	Formulation	Presentation	Volume	Lot Numbers
MenACWY-TT (GSK Biologicals)	MenA – tetanus toxoid (TT) conjugate 5 µg; MenC –TT conjugate 5 µg; MenW-135 –TT conjugate 5 µg; MenY –TT conjugate 5 µg; Tetanus toxoid (total) ~44 µg; Tris-HCL, pH 6.8 ± 0.3 1.6 mM; Sucrose 28 mg	Lyophilized: monodose vials, containing a white freeze dried pellet, were reconstituted before use with saline diluent (0.9% NaCl). Reconstituted vaccine was clear and colorless.	0.5 mL*	Vaccine: DMECA012A Diluent: AD02B254A
ActHIB (Sanofi Pasteur)	Polyribosylribitol phosphate (PRP) 10 µg; tetanus toxoid 24 µg; sucrose 8.5%	Lyophilized: monodose vials, containing a white freeze dried pellet were reconstituted before use with saline diluent (0.4% NaCl). Reconstituted vaccine was clear and colorless.	0.5 mL*	UF260AA UF292AA Diluent: UF336AB UF178AA
Pediarix (GSK Biologicals)	Diphtheria toxoid ≥30 IU (25 Lf), Tetanus toxoid ≥40 IU (10 Lf), Pertussis toxoid (PT) 25 µg, Filamentous haemagglutinin (FHA) 25 µg, Pertactin (PRN) 8 µg, Hepatitis B surface antigen (recombinant) 10 µg, Poliovirus type 1 (Mahoney) 40 D antigen units, Poliovirus type 2 (MEF-1) 8 D antigen units, Poliovirus type 3 (Saukett) 32 D antigen units, Aluminum adjuvant not more than 0.85 mg by assay, Residual formaldehyde ≤100 µg, Polysorbate 80 ≤100 µg, Sodium chloride 4.5 mg Neomycin ≤0.05 ng per dose Polymyxin B per dose ≤0.01 ng.	Liquid: pre-filled syringes containing a turbid white suspension.	0.5 mL	AC21B136C AC21B156D AC21B153B

Vaccine	Formulation	Presentation	Volume	Lot Numbers
Infanrix (GSK Biologicals)	Diphtheria toxoid ≥ 30 IU (25 Lf), Tetanus toxoid ≥ 40 IU (10 Lf), PT 25 µg, FHA 25 µg, PRN 8 µg Aluminum as salts 0.5 mg, 2-phenoxyethanol ≤ 2.5 mg	Liquid: pre-filled syringes containing a turbid white suspension.	0.5 mL	AC14B088A
Hib-MenCY-TT vaccine (GSK Biologicals)	*Haemophilus influenzae* type b polysaccharide (2.5 µg) conjugated to tetanus toxoid 5 to 7 µg; MenC –TT conjugate 5 µg; MenY –TT conjugate 5 µg; Tetanus toxoid (total) ~18 µg; Tris-HCL pH 6.8 1.6 mM; NaCl 150 mM Sucrose 12.6 mg	Lyophilized: monodose vials, containing a white freeze dried pellet, were reconstituted before use with saline diluent (0.9% NaCl). Reconstituted vaccine was clear and colorless.	0.5 mL*	DMEHA024B Diluent: AD02B211B AD02B136A AD02B239D1

* Entire contents of reconstituted vial were administered. Volume could have varied slightly among doses

Duration of treatment:
The intended duration of the study was approximately 19-22 months for each subject.

Criteria for evaluation:

Immunogenicity /efficacy:
Measurement of titers/concentrations of antibodies against study vaccine antigen components in blood samples using validated immunoassays in all subjects in each of the fourth dose study treatment groups as follows:

Primary endpoints:
One month after vaccination at 12-15 months of age
ACWY-TT group:
- hSBA-MenA, hSBA-MenW-135, hSBA-MenC, and hSBA-MenY titers ≥1:8
- hSBA-MenC and hSBA-MenY GMTs

Hib-CY group:
- hSBA-MenC and hSBA-MenY titers ≥1:8
- hSBA-MenC and hSBA-MenY GMTs

One month after vaccination at 15-18 months of age
Co-ad group and Control group:
- Anti-D concentrations ≥1.0 IU/mL
- Anti-T concentrations ≥1.0 IU/mL
- Anti-PT, anti-FHA and anti-PRN GMCs

Co-ad group:
- hSBA-MenA, hSBA-MenW-135, hSBA-MenC, and hSBA-MenY titers ≥1:8
- hSBA-MenC and hSBA-MenY GMTs

Secondary endpoints:
Immunogenicity
One month after vaccination at 12-15 months of age
MenACWY and Hib-CY groups:
- hSBA-MenC and hSBA-MenY antibody titers ≥1:4

MenACWY group:
- hSBA-MenA and hSBA-MenW-135 GMTs and antibody titers ≥1:4

Prior to vaccination at 15-18 months of age
Co-ad group
- hSBA-MenC and hSBA-MenY GMTs
- hSBA-MenC and MenY titers ≥1:4 and ≥1:8

One month after vaccination with *Infanrix* at 15-18 months of age
All treatment groups:
- Anti-D and anti-T GMCs
- Anti-PT, anti-FHA and anti-PRN concentrations ≥5 ELISA Units (EL.U)/mL
- Anti-D and anti-T seroprotection rates (antibody concentrations ≥0.1 IU/mL)

Co-ad group:
- hSBA- MenA, hSBA-MenW-135 GMTs
- hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY antibody titers ≥1:4

ACWY-TT and Hib-CY groups:
- Anti-D concentrations ≥1.0 IU/mL
- Anti-T concentrations ≥1.0 IU/mL
- Anti-PT, anti-FHA and anti-PRN GMCs

Safety
Secondary endpoints:
In all treatment groups:
Occurrence of solicited local and general symptoms on Days 0-7 after each vaccination in the Fourth Dose Phase
Occurrence of unsolicited symptoms up to one month (Days 0-30) after each vaccination in the Fourth Dose Phase
Occurrence from the first primary study dose up to/excluding the first Fourth Dose Phase visit (Visit 4) of serious adverse events (SAEs) and/or the specific AEs of:
- new onset of chronic illness(es) (e.g. autoimmune disorders, asthma, type 1 diabetes and allergies),
- conditions prompting ER visits.

Occurrence from the first Fourth Dose Phase visit (Visit 4) up to six months after the last vaccination of SAEs and/or the specific AEs of:
- new onset of chronic illness(es) (e.g. autoimmune disorders, asthma, type 1 diabetes and allergies),
- rash (e.g., hives, idiopathic thrombocytopenic purpura, petechiae) and/or conditions prompting emergency room (ER) visits.

Results Summary:

Demography:

The demographic profiles of the two groups in the Primary Total Vaccinated Cohort and of the four groups of subjects for the Fourth Dose ATP cohort for immunogenicity were comparable with respect to mean age, gender, ethnicity and racial distribution. The mean age at the start of the Fourth Dose Phase was 15.3 months, the male:female ratio was 1.03 and the population was predominantly of White - Caucasian/European heritage.

Immunogenicity /efficacy:

Immunogenicity analysis was performed on the ATP cohort (primary analysis) and on the Total vaccinated cohort.

Due to the hierarchy of the hypotheses and the fact that the pre-defined limit for non-inferiority was not reached for 2 out of 3 pertussis antigens in primary objective 4, care must be exercised in concluding that the pre-defined endpoints of primary objectives 5 and 6 were successfully achieved.

The results of the analyses of the co-primary objectives for this study are described below and are based on the analyses of the Fourth Dose ATP Cohort for immunogenicity.

Objective 1:

- The lower limit of the two-sided standardized asymptotic 95% CI for the group difference (ACWY-TT group Visit 5 blood sample minus Hib-CY group Visit 5 blood sample) in the percentage of subjects with hSBA-MenC titers ≥1:8 and hSBA-MenY titers ≥1:8 was -1.33% and -1.31%, respectively, above the pre-specified LL of ≥-10%.

Objective 1

Table 3s: Difference between ACWY-TT (Visit 5) and Hib-CY (Visit 5) groups in percentage of subjects with hSBA-MenC and hSBA-MenY titers equal to or above the cut-off values of 1:8 one month after the fourth dose (Fourth Dose ATP cohort for immunogenicity, Fourth Dose Phase)

								Difference in percentage (ACWY-TT minus Hib-CY)		
		ACWY-TT			Hib-CY				95% CI	
Antibody	Type	N	N	%	N	n	%	%	LL	UL
hSBA-MenC	1:8	286	286	100	155	155	100	0.00	-1.33	2.42
hSBA-MenY	1:8	291	291	100	157	157	100	0.00	-1.31	2.39
ACWY-TT = MenACWY-TT followed by *Infanrix* Hib-CY = Hib-MenCY-TT followed by *Infanrix* N = number of subjects with available results n/% = number/percentage of subjects with titer within the specified range 95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit										
The pre-defined statistical criteria pertaining to the objective of demonstrating non-inferiority of MenACWY-TT as compared to Hib-MenCY-TT with respect to the percentages of subjects with hSBA titers ≥1:8 for MenC and MenY was reached.										

Objective 1:

• The lower limit (LL) of the exact 95% CI for the ACWY-TT group in the percentage of subjects with hSBA-MenA titers ≥1:8 and hSBA-MenW-135 titers ≥1:8 one month after a dose of MenACWY-TT (Visit 5 blood sample) was 96.6% and 96.8%, respectively, which was above the pre-specified LL of ≥80.0%.

Objective 1:

Synopsis Table 4: Percentage of subjects in the ACWY-TT (Visit 5) group with MenA and MenW-135 hSBA titers equal to or above the cut-off values of 1:4 and 1:8 and GMTs (Fourth Dose ATP cohort for immunogenicity, Fourth Dose Phase)

				≥ 1:4				≥ 1:8			
						95% CI				95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	N	%	LL	UL
hSBA-MenA	ACWY-TT	PIV(M11)	257	256	99.6	97.9	100	254	98.8	96.6	99.8
hSBA-MenW-135	ACWY-TT	PIV(M11)	273	270	98.9	96.8	99.8	270	98.9	96.8	99.8

				GMT		
					95% CI	
Antibody	Group	Timing	N	value	LL	UL
hSBA-MenA	ACWY-TT	PIV(M11)	257	94.8	84.1	106.9
hSBA-MenW-135	ACWY-TT	PIV(M11)	273	923.9	776.0	1099.9

ACWY-TT = MenACWY-TT followed by *Infanrix*
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

The pre-defined statistical criteria pertaining to the objective of demonstrating immunogenicity of MenACWY-TT with respect to the percentages of subjects with hSBA titers ≥1:8 for MenA and MenW-135 was reached.

Since the criteria for MenC and MenY were reached as well as the criteria for MenA and MenW-135, the primary objective 1 is met.

Objective 2:

- The LL of the two-sided standardized asymptotic 95% CI for the group difference (Co-ad group Visit 7 blood sample minus Hib-CY group Visit 5 blood sample) in the percentage of subjects with hSBAMenC titers ≥1:8 and hSBA-MenY titers ≥1:8 was -1.30% and -1.25%, respectively, above the prespecified LL of ≥-10%.

Objective 2

Synopsis Table 5: Difference between Co-ad (Visit 7) and Hib-CY (Visit 5) groups in percentage of subjects with hSBA-MenC and hSBA-MenY titers equal to or above the cut-off values of 1:8 one month after the fourth dose (Fourth Dose ATP cohort for immunogenicity, Fourth Dose Phase)

								Difference in percentage (Co-ad minus Hib-CY)		
		Co-ad			Hib-CY				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
hSBA-MenC	1:8	293	293	100	155	155	100	0.00	-1.30	2.42
hSBA-MenY	1:8	303	303	100	157	157	100	0.00	-1.25	2.39

Hib-CY = Hib-MenCY-TT followed by *Infanrix*
Co-ad = MenACWY-TT + *Infanrix*
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

The pre-defined statistical criteria pertaining to the objective of demonstrating non-inferiority of MenACWY-TT co-administered with *Infanrix* as compared to Hib-MenCY-TT with respect to percentages of subjects with hSBA titers ≥1:8 for MenC and MenY was reached.

Objective 2:

Synopsis Table 6: Percentage of subjects in the Co-ad (Visit 7) group with MenA and MenW-135 hSBA titers equal to or above the cut-off values of 1:4 and 1:8 and GMTs (Fourth Dose ATP cohort for immunogenicity,Fourth Dose Phase)

				≥ 1:4				≥ 1:8			
						95% CI				95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	N	%	LL	UL
hSBA-MenA	Co-ad	PIV(M14)	258	253	98.1	95.5	99.4	248	96.1	93.0	98.1
hSBA-MenW-135	Co-ad	PIV(M14)	283	279	98.6	96.4	99.6	279	98.6	96.4	99.6

				GMT		
					95% CI	
Antibody	Group	Timing	N	value	LL	UL
hSBA-MenA	Co-ad	PIV(M14)	258	92.4	80.6	105.9
hSBA-MenW-135	Co-ad	PIV(M14)	283	1582.9	1321.8	1895.5

Co-ad = MenACWY-TT + *Infanrix*
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

The pre-defined statistical criteria of demonstrating immunogenicity of MenACWY-TT co-administered with *Infanrix* with respect to percentages of subjects with hSBA titers ≥1:8 for MenA and MenW-135 was reached.

Since the criteria for MenC and MenY were reached as well as the criteria for MenA and MenW-135, the primary objective 2 is met.

Objective 3:
• The LL of the two-sided standardized asymptotic 95% CI for the group difference (Co-ad group Visit 7 blood sample minus Control Visit 7 blood sample) in the percentage of subjects with anti-D and anti-T concentrations ≥1.0 IU/mL was -2.20% and -0.82%, respectively, above the pre-specified LL of ≥-10%.

Objective 3
Synopsis Table 7: Difference between Co-ad (Visit 7) and Control (Visit 7) groups in percentage of subjects with anti-T and anti-D concentrations equal to or above the cut-off values of 1.0 IU/mL one month after the fourth dose (Fourth Dose ATP cohort for immunogenicity, Fourth Dose Phase)

								Difference in percentage (Co-ad minus Control)		
		Co-ad			Control				95% CI	
Antibody	Type	N	n	%	N	N	%	%	LL	UL
Anti-T	1 IU/mL	253	253	100	146	145	99.3	0.68	-0.82	3.78
Anti-D	1 IU/mL	254	253	99.6	146	146	100	-0.39	-2.20	2.18

Co-ad = MenACWY-TT + *Infanrix*
Control = *Infanrix*
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

The objective of demonstrating non-inferiority of *Infanrix* co-administered with MenACWY-TT as compared to *Infanrix* alone with respect to percentages of subjects with antibody concentrations ≥1 IU/mL for anti-D and anti-T is met.

Objective 4:

- The LL of the two-sided standardized asymptotic 95% CI for the group ratios (Co-ad group Visit 7 blood sample minus Control Visit 7 blood sample) in GMCs was 0.71 for anti-FHA, above the pre-specified LL of 0.67. The LL of the two-sided standardized asymptotic 95% CI for the group ratios (Co-ad group Visit 7 blood sample minus Control Visit 7 blood sample) in GMCs for anti-PT (0.65) and anti-PRN (0.49) were below the pre-specified LL of 0.67.

Objective 4

Synopsis Table 8: GMC ratio between Co-ad (Visit 7) and Control (Visit 7) groups for anti-PT, anti-FHA and anti-PRN concentrations one month after a dose of *Infanrix* (Fourth Dose ATP cohort for immunogenicity, Fourth Dose Phase)

					GMC ratio (Co-ad / Control)		
	Co-ad		Control			95% CI	
Anti body	N	GMC	N	GMC	Value	LL	UL
Anti-PT	254	67.7	146	91.0	0.74	0.65	0.86
Anti-FHA	253	353.2	146	422.9	0.84	0.71	0.98
Anti-PRN	253	189.2	146	315.1	0.60	0.49	0.73

Co-ad = MenACWY-TT + *Infanrix*
Control = *Infanrix*
GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

• The pre-defined statistical criteria pertaining to the primary objective of non-inferiority of the MenACWY-TT vaccine co-administered with *Infanrix* as compared to *Infanrix* alone with respect to anti-PT and anti-PRN GMCs was not reached. The statistical criterion for non-inferiority for FHA was reached.
• Since the criterion for anti-PT and for anti-PRN was not reached, the primary objective 4 of non-inferiority is not met.

Assessor's comment: Because of the hierarchical testing, following a failure of 2/3 results for objective 4 to meet non-inferiority, objectives from 5 onwards cannot be considered to have been met.

Objective 5:

- The LL of the two-sided standardized asymptotic 95% CI for the group ratios (ACWY-TT group Visit 5 blood sample over the Hib-CY group Visit 5 blood sample) in GMTs was 1.11 for hSBA-MenC and 1.71 for hSBA-MenY, above the pre-specified LL of 0.5.

Objective 5

Synopsis Table 9: GMT ratio between ACWY-TT (Visit 5) and Hib-CY (Visit 5) groups for hSBA-Men and hSBA-MenY titers one month after the fourth dose (Fourth Dose ATP cohort for immunogenicity, Fourth Dose Phase)

					GMT ratio (ACWY-TT / Hib-CY)		
	ACWY-TT		Hib-CY			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
hSBA-MenC	286	3845.016	155	2676.138	1.44	1.11	1.87
hSBA-MenY	291	4800.911	157	2227.703	2.16	1.71	2.71

ACWY-TT = MenACWY-TT followed by *Infanrix*
Hib-CY = Hib-MenCY-TT followed by *Infanrix*
GMT = geometric mean antibody titer
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

- The pre-defined statistical criteria pertaining to the objective of demonstrating the non-inferiority of MenACWY-TT as compared to Hib-MenCY-TT with respect to MenC and MenY hSBA GMTs was reached. However, as the objectives are hierarchical and the previous objective was not met, we cannot conclude that this objective had been met.

Objective 6:

- The LL of the two-sided standardized asymptotic 95% CI for the group ratios (Co-ad group Visit 7 blood sample over the Hib-CY group Visit 5 blood sample) in GMTs was 2.08 for hSBA-MenC and 2.72 for hSBA-MenY, above the pre-specified LL of 0.5.

Objective 6

Synopsis Table 10: GMT ratio between Co-ad (Visit 7) and Hib-CY (Visit 5) groups for hSBA-MenC and MenY titers one month after the fourth dose (Fourth Dose ATP cohort for immunogenicity, Fourth Dose Phase)

					GMT ratio (Co-ad / Hib-CY)		
	Co-ad		Hib-CY			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
hSBA-MenC	293	7230.524	155	2676.138	2.70	2.08	3.50
hSBA-MenY	303	7487.605	157	2227.703	3.36	2.72	4.15

Co-ad = MenACWY-TT + *Infanrix*
Hib-CY= Hib-MenCY-TT followed by *Infanrix*
GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

- The pre-defined statistical criteria pertaining to the objective of demonstrating the non-inferiority of MenACWY-TT co-administered with *Infanrix* as compared to Hib-MenCY-TT with respect to MenC and MenY hSBA GMTs was reached.
- Because of the hierarchical order, objective 6 has not been met.

As the objectives were assessed in a hierarchical manner, co-primary objectives 1 to 3 were met and objectives 4 to 6 were not met.

Safety /reactogenicity:
The primary analysis of safety was performed on the Fourth Dose Total vaccinated cohort. Since more than 5% of the enrolled subjects were eliminated from the Fourth Dose ATP cohort for safety, an additional analysis was performed on the ATP cohort for safety to support the analysis of the Fourth Total vaccinated cohort.

Overall incidence of AEs:
• During the 4-day follow-up period, at least one symptom (solicited or unsolicited) was reported after the fourth dose in 75% of subjects in the ACWY-TT group, 76.0% of subjects in the Hib-CY group, 80.4% of subjects in the Co-ad group and 76.0% of subjects in the Control group and after the fifth dose in 71.0% of subjects in the ACWY-TT and 73.0% of subjects in the Hib-CY group

Solicited local AEs:
Redness was the most frequently reported solicited local symptoms during the 4-day follow-up period after the fourth dose in the ACWY-TT (41.9%), Co-ad (53.4%) and Control (57.1%), and after the fifth dose in the ACWY-TT (45.5%) and Hib-CY (51.8%) groups. Pain was the most frequently reported solicited local symptom during the 4-day follow-up period after the fourth dose in the Hib-CY group (47.9%).

Solicited general AEs:
Irritability was the most frequently reported general adverse event during the 4-day follow-up period after each dose in all groups (≥47.9% of subjects). Fever was reported in 3.8% to 7.8% of subjects during the 4- day follow-up period after the fourth dose in all groups, and in 6.5% and 5.6% of subjects after the fifth dose in the ACWY-TT and Hib-CY groups respectively.

Unsolicited AEs:
Unsolicited adverse events during the 31-day (Days 0-30) post-dose 4 were reported for 194 (44.9%), 105 (45.9%), 182 (44.5%), and 101 (43.3%) subjects in the ACWY-TT group, Hib-CY group, Co-ad group, and Control group, respectively. Unsolicited adverse events during the 31-day (Days 0-30) post-dose 5 period in the ACWY-TT groups and Hib-CY group were reported for 167 (38.7%) and 79 (34.5%) subjects respectively. Grade 3 symptoms were infrequent, reported in 0.9%-5.7% of subjects following the fourth dose, and in 2.3% - 2.6% of subjects in the ACWY-TT and Hib-CY groups following the fifth dose.

Specified AEs:
Overall, at least one SAE, NOCI, rash, or emergency room visit from Visit 1 up to 6 months after last vaccination in the Fourth Dose Phase was reported for 56.7%, 61.1%, 55.3% and 45.1% for the ACWY-TT, Hib-CY, Co-ad and Control groups, respectively.

Serious adverse events:
SAEs were reported for 30 (6.9%), 11 (4.8%), 26 (6.4%), and 10 (4.3%) subjects in the ACWY-TT group, Hib-CY group, Co-ad group, and Control group, respectively from the first dose of Primary Phase up to 6 months after the last vaccination. A total of three of the SAEs, one subject (Floppy Infant) in the Co-ad group, Fourth Dose Phase and one subject with two SAEs [Sudden Infant Death Syndrome (SIDS) and Convulsion] in the Hib-CY group, Primary Phase, were considered by the investigators as potentially related to vaccination. Four subjects reported a total of seven fatal SAEs, all in the Hib-CY primary group: one subject reported leukaemia and subsequent respiratory failure: two subjects reported SIDS; and one subject reported septic shock, dehydration, and haemolytic uraemic syndrome. No fatal SAEs were reported during the Fourth Dose Phase.

Assessor's comment: The case of floppy infant occurred at the fourth dose phase of the trial in the Co-Ad group was grade 3, lasted 2 days and resolved. Although Study 0-57 was not available at the time of MAA, this case was described in the original MAA.

Withdrawals due to adverse events /serious adverse events:
Adverse events led to premature discontinuation/withdrawal from the Primary Phase in 6 subjects: four, due to a serious adverse event (two reports of SIDS, one subject with dehydration, haemolytic uraemic syndrome and septic shock and one subject with dysphagia and hypotonia, all Hib-MenCY-TT recipients) and two due to non-serious adverse events (one subject with neutropenia and one subject with hypotonia, both Hib-MenCY-TT recipients). Adverse events led to premature discontinuation/withdrawal from the Fourth Dose Phase in 2 subjects: one due to a serious adverse event (febrile convulsion in a Hib-MenCY-TT recipient) and one due to non-serious adverse event (febrile convulsion in a MenACWY-TT recipient).

MAH Conclusion(s):
1. MenACWY-TT vaccine administered in the ACWY-TT group was non-inferior to the Hib-CY group with regard to percentage of subjects with hSBA titers ≥1:8 for MenC and MenY and was immunogenic for MenA and MenW-135
2. MenACWY-TT vaccine administered together with *Infanrix* in the Co-ad group was non-inferior to the Hib-CY group with regard to percentage of subjects with hSBA titers ≥1:8 for MenC and MenY and was immunogenic for MenA and MenW-135
3. *Infanrix* administered together with MenACWY-TT in the Co-ad group was non-inferior to the Control with regard to percentage of subjects with anti-D and anti-T concentrations ≥1.0 IU/mL
4. *Infanrix* administered together with MenACWY-TT in the Co-ad group did not reach non-inferiority criteria as compared to the Control with regard to GMCs for anti-PT and anti-PRN. The pre-defined statistical criterion for non-inferiority for FHA was reached. However, since not all the pre-defined statistical criteria were met, objective 4 was not met.
5. The GMT ratio between the ACWY-TT group and (over) the Hib-CY group reached predefined statistical criteria for non-inferiority for MenC and MenY.
6. The GMT ratio between the Co-ad group and (over) the Hib-CY group reached predefined statistical criteria for non-inferiority for MenC and MenY.
As the objectives were assessed in a hierarchical manner, co-primary objectives 1 to 3 were met and objectives 4 to 6 were not met.
Unsolicited adverse events during the 31-day (Days 0-30) post-dose 4 period were reported for 194 (44.9%), 105 (45.9%), 182 (44.5%), and 101 (43.3%) subjects in the ACWY-TT group, Hib-CY group, Co-ad group, and Control group, respectively.
Unsolicited adverse events during the 31-day (Days 0-30) post-dose 5 period in the ACWY-TT groups and Hib-CY group were reported for 167 (38.7%) and 79 (34.5%) subjects administered MenACWY-TT and Hib-Men-CY-TT, respectively.
At least one specific symptom (SAE, new onset chronic illness, rash, and/or emergency room visit) throughout the study from the time of enrollment up to 6 months after the last vaccination (Primary and Fourth Dose Phases) was reported for 245 (56.7%), 140 (61.1%), 226 (55.3%), and 105 (45.1%) subjects in the ACWY-TT group, Hib-CY group, Co-ad group, and Control group, respectively.
SAEs were reported for 30 (6.9%), 11 (4.8%), 26 (6.4%), and 10 (4.3%) subjects in the ACWY-TT group, Hib-CY group, Co-ad group, and Control group, respectively from the first dose of Primary Phase up to 6 months after the last vaccination.
A total of three of the SAEs, one subject (Floppy Infant) in the Co-ad group, Fourth Dose Phase and one subject with SIDS and Convulsion in the Hib-CY group, Primary Phase, were considered by the investigators as potentially related to vaccination.
Seven fatal SAEs, all in the Hib-CY primary group were reported: one subject reported leukaemia and subsequent respiratory failure: two subjects reported SIDS and one subject reported septic shock, dehydration, and haemolytic uraemic syndrome. No fatal SAEs were reported during the Fourth Dose Phase.
In this study, all vaccination regimens were well tolerated.

Summary from expert report:

The purpose of the study was to evaluate the safety and immunogenicity of Nimenrix when administered as a fourth vaccination (at 12-15 or 15-18 months of age) against meningococcal serogroups C and Y in the second year of life after priming with Menhibrix at 2, 4 and 6 months of age. Since in the US a fourth dose of Diptheria-tetanus-acellular pertussis (DTaP) vaccine is recommended at 15-18 months of age, this study also provide data on the co-administration of Infanrix with Nimenrix. Non-inferiority with respect to the immunogenicity of Infanrix co-administered with Nimenrix as compared to Infanrix administered alone was evaluated. All subjects were primed with Pediarix at 2, 4 and 6 month of age as part of the study.

When Nimenrix was administered at 12-18 months of age the serogroups A and W-135 antigens were administered as the primary dose; therefore this study also evaluated the immunogenicity of Nimenrix administered at 12-18 months of age with respect to serogroups A and W-135 given as a primary dose.
Of interest and relevant to the approved indication of Nimenrix in the EU this study also evaluated the immunogenicity of Nimenrix administered at 12-15 and 15-18 months of age with respect to serogroups C and W-135 given as a primary dose.
One month after vaccination with Nimenrix at 12-15 months of age (ACWY-TT group) and one month after co-administration of Nimenrix with Infanrix at 15-18 months of age (Co-ad group) the percentage of subjects with

hSBA titres ≥ 1:8 for MenA were 98.8% and 96.1% respectively. The hSBA MenA GMTs were 94.8 and 92.4 in the ACWY-TT and Co-ad groups respectively, suggesting no impact of age at vaccination on immunogenicity against MenA as measured by hSBA. The hSBA MenW-135 GMTs were 923.9 and 1582.9 in the ACWY-TT and Co-ad groups respectively which suggested higher immunogenicity in the group that received Nimenrix at 15-18 months of age. However the clinical relevance of this observation is unclear given the percentage of subjects with hSBA titres ≥ 1:8 for W-135 were similar (i.e. 98.6% and 98.9% in the ACWY-TTT and Co-ad groups respectively).

. The purpose of the study was to evaluate the safety and immunogenicity of Nimenrix when administered as a fourth vaccination (at 12-15 or 15-18 months of age) against meningococcal serogroups C and Y in the second year of life after priming with Menhibrix at 2, 4 and 6 months of age. Since in the US, a fourth diphtheria-tetanus-acellular pertussis (DTaP) vaccine is recommended at 15-18 months of age, this study also provides data on co-administration of Infanrix with Nimenrix.
. Of interest and relevant to the approved Nimenrix indication in the EU this study also evaluated the immunogenicity of Nimenrix administered at 12-15 and 15-18 months of age with respect to serogroups A and W-135 given as a primary dose. One month after vaccination with Nimenrix at 12-15 months of age (ACWY-TT group) and one month after co-administration of Nimenrix with Infanrix at 15-18 months of age (Co-ad group) the percentage of subjects with hSBA titres ≥1:8 for MenA were 98.8% and 96.1% respectively. The hSBA MenA GMTs were 94.8 and 92.4 in the ACWY-TT and Co-ad groups respectively, suggesting no impact of age at vaccination on immunogenicity against MenA as measured by hSBA.
. In this study non-inferiority of the response induced by Infanrix hexa co-administered with Nimenrix compared to the one induced by Infanrix hexa alone was demonstrated, given that the lower limit of the two-sided 95% CI on the adjusted GMC ratios for anti-PT, anti-FHA and anti-PRN were above the success criterion defined by the protocol >0.67 (0.83; 0.85 and 0.78 respectively). These observations are not in line with what has been reported in phase III study MenACWY-TT-040 which evaluated non-inferiority of Nimenrix and Infanrix hexa co-administration compared to administration of both vaccines alone and which was included in the original MAA.
In the currently ongoing study MenACWY-TT-083 in infants evaluation of immunogenicity of Infanrix hexa when co-administered with Nimenrix according to 2, 3, 4 and 12 months and 2, 4 and 12 months schedules is planned. This study will provide further data with regards to potential interactions between Nimenrix and Infanrix hexa antigens and the results will be provided when they become available.

Assessor's comment: The relevance of this study to the product information in the EU is limited as all subjects given Nimenrix between 12-18 months of age were previously primed with Menhibrix which is not available in the EU and co-administered vaccines followed the US schedules. The MAH proposes no change to the SmPC following the data from this study and this is agreed.
Study MenACWY-TT-083 this will provide more information on immunogenicity of Infanrix hexa when co-administered with Nimenrix according to 2, 3, 4 and 12 months and 2, 4 and 12 months schedules

Note:
A variation application consisting of the full relevant data package (i.e containing several studies to update the labelling with available persistence data) is expected to be submitted by the beginning of 2013.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

The MAH has submitted data in accordance with Article 46 for the following procedures
P46 008 (MENACWY-TT-018 EXT:015 Y3) seq 11
P46 009 (MENACWY-TT-030 EXT:027 Y3) seq 12
P46 014 (MENACWY-TT-031 EXT 027 Y4) seq 19
P46 010 (MENACWY-TT-048 EXT: 039 Y2,3,4,5) seq 13
P46 011 (MENACWY-TT-071) seq 14
P46 012 (MENACWY-TT-057 PRI AND 057-BST) seq 15

For P46 008, 009 and 010 the data consisted of Year 3 follow-up data on immunogenicity and safety from the original studies. The data provided for Art 46 014 was a Year 4 follow-up on persistence of immunogenicity from the previous study. In the case of Art 011 and Art 012, stand alone studies were provided.
The MAH is collecting further more comprehensive data, and plan to submit a variation at the beginning of 2013.
No SmPC changes are required following from these article 46 procedures.

➢ Recommendation

No further action required.